Choledocholithiasis: An update on current evidence and practice

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Abstract

Introduction

Gallstone disease and its complications place a substantial burden on healthcare services, with common bile duct calculi having the potential to cause significant morbidity and mortality, particularly following the occurrence of ascending cholangitis or pancreatitis. Due to these potential risks it is important, when present, to accurately identify common bile duct calculi in patients with gallstone disease. There are a number of investigations available to aid clinicians in the identification of choledocholithiasis. The aim of this review is to evaluate the current evidence and the up-to-date practice within western populations.

Methods

A literature review was performed using the Medline database.

Conclusion

The reliability of trans-abdominal ultrasound scans and liver function tests in accurately identifying common bile duct calculi were found to be poor. Risk stratification using algorithms incorporating both tests, together with clinical factors, were also found to be inadequate for accurately predicting choledocholithiasis. Based on initial screening further assessment in intermediate and high-risk groups is suggested to avoid unnecessary invasive investigations and therapeutic procedures, which themselves are associated with a significant rate of complications.

Key words: Choledocholithiasis, Serology, USS, MRCP, ERCP

1. Introduction

Gallstone disease represents a significant burden for healthcare services, particularly in western populations, with an estimated adult disease prevalence in the United States of 10-15%[1]. The spectrum of disease severity varies considerably from self-limiting attacks of biliary colic and cholecystitis to ascending cholangitis and gallstone pancreatitis, both of which are associated with significant morbidity and may be life-threatening in severe cases[2,3]. These conditions are inherently linked to the presence or passage of common bile duct (CBD) calculi[4]. Therefore the accurate identification or exclusion of choledocholithiasis, as part of the assessment of a patient with gallstone disease, is of crucial importance. There are a number of investigations currently used to predict choledocholithiasis that have variable sensitivities and specificities. The challenge is to find a predictive test that is both cost-effective and reliable. The aim of this review is to appraise the current evidence and best practice guidelines in the evaluation of patients with suspected choledocholithiasis. Our review is targeted at the management of patients in western populations, in which the resources and expertise are usually available to allow incorporation of the optimal investigative modalities as described in the literature.

2. Background

The investigation of a patient with suspected gallstone disease encompasses the use of serological, radiological and endoscopic modalities, some of which are more invasive than others. During initial assessment, all patients will have serological markers measured (including liver function tests and amylase), together with trans-abdominal ultrasonography (USS) of the biliary tract. Further investigation, depending on available resources and expertise, may include magnetic resonance cholangio-pancreatography (MRCP), endoscopic ultrasonography (EUS), intraoperative cholangiography (IOC) or endoscopic retrograde cholangiopancreatography (ERCP). In the context of a patient with gallstone disease derangement of liver function tests (LFTs), specifically elevations in serum bilirubin, alanine transaminase (ALT), alkaline phosphatase (ALP) and gamma-glutamyl transferase (GGT) can be indicative of CBD calculi. A rise in ALP and/or bilirubin is generally accepted as more suggestive of obstructive jaundice, compared with elevations in the other enzymes. Similarly, dilated intra or extra-hepatic ducts and/or a dilated CBD demonstrated on ultrasonography may also be indicative of CBD calculi. Direct visualisation of the CBD is often difficult using ultrasonography. However, when the CBD is clearly seen, particularly in a thin patient, the diagnosis of CBD calculi is possible, although it is important to recognise the operator dependent nature of the procedure and the significant heterogeneity in the skill mix of operators which determines its diagnostic accuracy.

The benefits of both serological tests and ultrasonography are that they are non-invasive, inexpensive and generally readily available which allows repeat and serial investigations if indicated. Unfortunately, the reliability of these tests when used either alone or in combination, when attempting to exclude or diagnose CBD calculi (without further non-invasive testing), is often inadequate and could lead to unnecessary invasive diagnostic and/or therapeutic interventions. Furthermore, a false negative result can mislead clinicians by providing inappropriate reassurance leading to delayed treatment and

potentially significant consequences in the form of pancreatitis or cholangitis. Algorithms for the further management of patients with suspected choledocholithiasis have been developed utilising ultrasonography, liver function tests and clinical parameters to assess the risk of a patient having CBD calculi. Of the various algorithms available the classification system proposed by the American Society for Gastrointestinal Endoscopy (ASGE)[5] in 2010 has perhaps been the most widely adopted. The ASGE classification categorises patients into low, intermediate and high risk groups based on the presence or absence of eight clinical predictors, with these clinical predictors being further divided into moderate, strong and very strong (table 1).

High risk patients are deemed to be those with the presence of any very strong predictor or the presence of both strong predictors. Low risk patients are those in whom no predictors are present. All other patients are deemed to be intermediate risk. In high risk groups the probability for the presence of CBD calculi is predicted to be >50%, with intermediate and low risk groups having probabilities of 10-50% and <10% respectively. In high risk groups, the ASGE guidelines have suggested ERCP without further non-invasive testing, due to the "high probability of choledocholithiasis and the frequent need for therapeutic intervention". In intermediate risk groups, further testing in the form of pre-operative MRCP or EUS has been suggested. Alternatively, intra-operative cholangiography or laparoscopic ultrasonography prior to cholecystectomy has also been suggested in intermediate risk groups depending on the available resources. In low risk groups, no further investigation is suggested prior to performing cholecystectomy in patients who are suitable for surgery.

Authors of the ASGE classification commented that at the time of publication the guideline was "not a validated clinical decision aid" and the concept of performing ERCP in high risk patients deemed to have a probability of as little as 50% for CBD calculi would not be acceptable to the majority of clinicians, given the potentially significant risks involved in performing the procedure.

Current practice within our centre is to perform MRCP on all patients with gallstones who have derangements in liver function tests and/or a dilated biliary tree shown on trans-abdominal USS. In addition to this we perform a repeat USS by a consultant radiologist or an MRCP if the patient has persistently raised LFTs with a normal initial USS. Although the use of MRCP is resource dependent, it is a non-invasive test with very low patient risk in comparison to EUS and ERCP, and has a very high diagnostic accuracy for choledocholithiasis, comparable to both EUS and ERCP. MRCP has been demonstrated to have up to 97% specificity for detecting choledocholithiasis although its accuracy is reduced when small calculi (<5mm) are present[6]. The use of ERCP as a diagnostic investigation is never performed within our institution and its use is reserved only for therapeutic intervention, once a diagnosis of choledocholithiasis has been confirmed following definitive imaging of the biliary tree.

Various further strategies were suggested in the ASGE guidelines including sequential EUS and ERCP, whereby high-risk patients on initial triaging would only undergo ERCP if CBD calculi were confirmed by a pre-procedure EUS. Given the high negative

predictive value of EUS[7], this strategy would considerably limit the amount of unnecessary ERCP procedures in high risk groups who had not undergone further non-invasive testing to confirm choledocholithiasis, as suggested by the ASGE guidelines. However, the expertise and resources to perform EUS directly prior to ERCP, in high-risk patients with unconfirmed CBD calculi, may not be available in all institutions and the use of EUS still carries the risk of undergoing an endoscopic procedure. Within our centre, the use of EUS is limited to a specific subset of patients in whom trans-abdominal ultrasonography has not demonstrated gallstones but there is a clinical suspicion of microlithiasis.

3. Method

A search was conducted using the Medline database to identify relevant literature relating to the investigation and management of patients with suspected choledocholithiasis. As mentioned previously, current practice within our centre is to perform definitive imaging of the biliary tree using MRCP, in patients with a high clinical suspicion of choledocholithiasis following initial triaging with LFT measurements and trans-abdominal ultrasonography. The main objective of our review was to assess the accuracy of predicting choledo-cholithiasis using LFTs and trans-abdominal ultrasonography in order to define a subset of patients in whom MRCP can be safely avoided. We also assessed the validity of the current ASGE guidelines, in particular the concept of performing ERCP in those patients defined as "high risk" without prior confirmatory biliary tract imaging. Search terms included: common bile duct calculi, choledocholithiasis, liver function tests, ultrasonography, MRCP/magnetic reso-nance cholangiopancreatography, ERCP/ endoscopic retrograde cholangio-pancreatography, endoscopic ultrasound and intraoperative cholangiography. Following exclusion of unsuitable and duplicate studies a total of 76 abstracts were selected for further review, of which 12 full text studies were selected for inclusion and review (figure 1).

4. Results

The reported diagnostic accuracy of ultrasonography and LFTs for choledocholithiasis varies in the literature and perhaps the most robust recent publication evaluating their use was a Cochrane review published in 2015 conducted by *Gurusamy et al*[8]. In total, five studies were included for review. The cumulative sensitivity for ultrasonography in diagnosing CBD calculi was found to be 0.73 (95% CI 0.44 to 0.90) and the cumulative specificity for ultrasonography was found to be 0.91 (95% CI 0.84 to 0.95). There was only one study included that concomitantly assessed the use of LFTs (Table 2). Authors concluded that further diagnostic tests are required with positive USS or deranged LFTs to confirm or refute CBD calculi and similarly, negative tests with persistent symptoms should prompt further investigations.

In a retrospective study conducted in 2014, *Isherwood et al*[9] demonstrated a statistically significant association with persistently deranged LFTs and CBD calculi proven on MRCP, with the greatest association demonstrated for ALT (OR 5.4, $P<0.001$). A statistically significant association was also found with a dilated CBD and dilated intrahepatic ducts shown on USS (OR 5.56 and 3.76 respectively, $P<0.001$). This study concluded that persistent derangements in LFT's should prompt definitive imaging of the biliary tree to evaluate for the presence of CBD

calculi. Similarly, a retrospective review conducted by *Ahn et al*[10] in 2016 found an association with persistent derangement of LFT's and CBD calculi in patients with concurrent acute cholecystitis. *Ahn et al* also found GGT to be the LFT with the highest predictive value for choledocholithiasis in patients with acute cholecystitis (sensitivity 0.80 and specificity 0.75 at an optimal cut off of 224 IU/L, P<0.001). A dilated CBD on USS was conversely shown to be a poor predictor of choledocholithiasis for patients with concurrent acute cholecystitis in a study conducted by *Boys et al*[11]in 2014. In support of these findings a study conducted by *Qiu et al*[12] in 2015 concluded that the use of USS was unreliable in the pre-operative screening of patients for choledocholithiasis with a detection rate of 55.05% .

Two separate retrospective studies, conducted by *Rubin et al*[13] in 2013 and *Magalhães et al*[14] in 2014, assessed the accuracy of ultrasonography and liver function tests in diagnosing choledocholithiasis. Both studies used the reference values and examination findings as defined by the ASGE classification's predictors of choledocholithiasis. *Rubin et al* demonstrated a statistically significant correlation for choledocholithiasis demonstrated on trans-abdominal USS and subsequent choledocholithiasis confirmed on ERCP (P=0.00179). There was also a statistically significant correlation demonstrated with a dilated CBD on trans-abdominal USS and bilirubin levels >4mg/dl (P=<0.05). Similarly, *Magalhães et al* found there to be a statistically significant correlation for choledocholithiasis confirmed on ERCP with all predictors (apart from gallstone pancreatitis) including CBD calculi on trans-abdominal USS (P=<0.001), bilirubin levels >4mg/dl (P=0.035), and a dilated CBD on trans-abdominal USS (P=<0.001).

Five of the reviewed studies assessed the use of the ASGE classification for the assessment of patients with suspected choledocholithiasis. Both *Rubin et al*[13] and *Magalhães et al*[14] concluded that although there were statistically significant associations demonstrated with the majority of predictors, their value in accurately stratifying risk were inadequate (due to their poor and unreliable sensitivity and specificity profiles) to preclude the need for further testing prior to invasive interventions, especially in those deemed to be high risk. A study conducted by *Prachayakul et al*[15] in 2014 also concluded that the ASGE predictors were inaccurate in predicting the presence of CBD calculi in intermediate and high risk groups. *Narváez-Rivera et al*[16] conducted a prospective review assessing the accuracy of the ASGE predictors in intermediate and high risk groups as defined by the ASGE classification. All patients included in the study underwent ERCP. The findings demonstrated poor results in both groups, with 41% of patients having choledocholithiasis on ERCP in the intermediate group and 59% of patients in the high-risk group. Overall, 43% of patients underwent unnecessary ERCP procedures, a figure which most clinicians would agree is unacceptable in a modern healthcare setting. A study conducted by *Anand et al*[17] in 2015 supported the use of ERCP in high risk groups without further non-invasive testing as suggested by the ASGE guidelines. This study found there to be statistically significant longer inpatient stays, time to ERCP procedures (72 VS 35 hours) and higher hospital charges with the use of MRCP prior to ERCP in high-risk groups. All patients in this study

underwent ERCP regardless of MRCP findings and, in the twenty patients with normal MRCP findings, five patients were found to have subsequent CBD calculi on ERCP with a further four patients having CBD sludge. This study raises important questions as ERCP is not without risk and eleven patients would have undergone an unnecessary ERCP procedure. Furthermore, given the delay in performing ERCP procedures in the patients that underwent MRCP, it is also feasible that those patients with normal MRCPs who subsequently had calculi demonstrated on ERCP may have had de-novo passage of calculi that were not present on prior imaging.

The investigative options available for patients with suspected choledocholithiasis, following initial triaging with LFT measurements and trans-abdominal USS, include MRCP, EUS, IOC or diagnostic ERCP depending on available resources. Both MRCP and EUS are regarded to be non-invasive and minimally invasive tests respectively, with EUS involving the risks of an endoscopic procedure. IOC and ERCP are advantageous in that they can be performed directly prior to therapeutic interventions, ether by surgical CBD exploration/clearance or endoscopic CBD clearance/stent placement respectively. A Cochrane systematic review conducted by *Giljaca et al*[7] in 2015 found there was a high diagnostic accuracy for choledocholithiasis using both MRCP and EUS, with no statistically significant difference demonstrated when comparing the sensitivities and specificities of both tests (P=0.5). Authors advocated either surgical or endoscopic CBD clearance following positive EUS or MRCP procedures. Authors also recommended that patients with negative EUS or MRCP procedures did not need further investigations, provided there was resolution of symptoms. Similarly, in a retrospective study evaluating the utility of EUS, *Prachayakul et al*[15] also found there to be a high diagnostic accuracy of EUS in diagnosing CBD calculi.

ERCP and IOC are not regarded as first line tests in the investigation of patients with suspected choledocholithiasis, with their use generally reserved for patients where there is a high suspicion of choledocholithiasis or when choledocholithiasis has been confirmed with other non-invasive tests such as EUS or MRCP. The choice of procedure will usually be dependent on the clinicians' expertise and preference for subsequent therapeutic intervention, with ERCP being performed to clear the CBD most commonly prior to undertaking laparoscopic cholecystectomy and IOC being performed during cholecystectomy with subsequent surgical CBD exploration and clearance.

Within our centre, the majority of patients will undergo ERCP, following confirmatory imaging with MRCP, to clear the CBD prior to cholecystectomy. The use of IOC immediately prior to cholecystectomy is generally reserved for those patients with a suspicion of choledocholithiasis in whom MRCP cannot be performed. A Cochrane systematic review conducted by *Gurusamy et al*[18] in 2015 compared the accuracy of IOC and ERCP in the diagnosis of choledocholithiasis and found there to be weak evidence supporting a higher sensitivity of IOC over ERCP (summary sensitivity 0.99 VS 0.83, P=0.05). No difference was found in specificity between the two tests (summary specificity 0.99 VS 0.99, P=0.7).

5. Conclusion

Although derangements in liver function tests and abnormalities on ultrasonography have been shown to have statistically significant associations with choledocholithiasis, their use as diagnostic tests are limited due to their unreliable sensitivity and specificity, a finding which has been consistently demonstrated in the literature and summarised in this review. Algorithms combining USS and LFTs findings, together with clinical factors, can facilitate risk stratification of patients, guiding further diagnostic tests and therapeutic interventions. However, the majority of studies examined in our literature review demonstrated that the accuracy of predicting choledocholithiasis in high risk groups was inadequate, without conducting further non-invasive tests to confirm a diagnosis, prior to performing therapeutic interventions or invasive diagnostic testing.

Incorporating the use of MRCP or EUS in intermediate and high risk groups would allow a greater accuracy in identifying patients that need further therapeutic interventions. By definition, patients with an intermediate or high risk of choledocholithiasis, as defined by the ASGE classification, would include those with abnormal LFT parameters and a dilated biliary tree on trans-abdominal USS. Therefore, our current practice of performing MRCP in these patients is consistent with the above approach. Also, given the user dependent nature of trans-abdominal ultrasonography and the difficulties encountered in accurately visualising the entire common bile duct in many patients, it may also be prudent to perform confirmatory MRCP in those patients with CBD calculi demonstrated on transabdominal ultrasonography if there are any doubts regarding reliability. The inevitable additional costs and delays in patient management with this strategy may be offset by the cost saving resulting from the reduced number of patients requiring therapeutic interventions. More importantly, it would also limit the number of patients exposed to unnecessary invasive interventions, the potential risks of which can be substantial and result in significant patient morbidity and occasional mortality with the consequent impact on healthcare resources. In addition, we have been unable to identify a specific subset of intermediate risk patients with a low enough predicted risk for choledocholithiasis based on initial triaging with LFT measurements, clinical factors or trans-abdominal ultrasonography, where MRCP can be safely avoided. Additional well-designed randomised trials are required to determine whether such a group exists.

Tables and figures:

Predictors of Choledocholithiasis
Very strong predictors: • **CBD calculi demonstrated on ultrasonography** • **Clinical diagnosis of cholangitis** • **Bilirubin levels >4mg/dl**
Strong predictors: • **Dilated CBD on ultrasonography (>6mm in patients with a gallbladder in-situ)** • **Bilirubin levels between 1.8 and 4mg/dl**
Moderate predictors: • **Abnormal LFT test/s other than bilirubin** • **Age >55 years** • **Clinical diagnosis of gallstone pancreatitis**

Table 1: Clinical, serological and radiological predictors of Choledocholithiasis, adapted from ASGE classification, 2010[5].

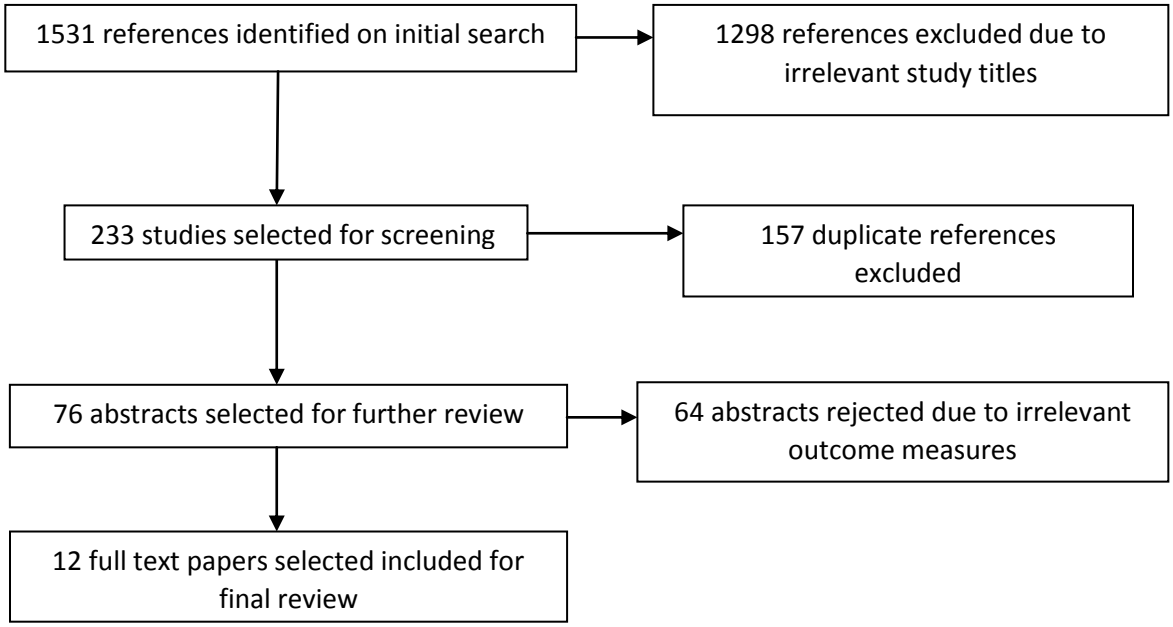

Figure 1: Flow chart of study selection.

Article	Study Design	Results	Conclusions
Isherwood et al (2014)[9]	• Retrospective review of patients undergoing MRCP for suspected choledocholithiasis between 2005 & 2011 (N=195). • 71 patients identified as having CBD calculi on MRCP. • LFTs at admission and prior to MRCP were analysed. • Ultrasound findings prior to MRCP were analysed.	• Statistically significant correlation for persistently raised LFTs taken prior to MRCP and choledocholithiasis on MRCP (ALT: OR 5.40, P<0.001, ALP: OR 4.64, P<0.001, bilirubin OR 2.02, P<0.025). • Statistically significant correlation of a dilated CBD and intrahepatic duct dilatation with choledocholithiasis on MRCP (OR 3.76, P<0.001 and OR 5.56, P<0.001 respectively). • Poor sensitivities and specificities demonstrated for LFTs at both admission and prior to MRCP.	• Persistent derangement of LFT parameters in patients with suspected choledocholithiasis, with a normal USS should prompt definitive imaging of the biliary tree.
Gurusamy et al (2015)[8]	• Cochrane systematic review analysing the accuracy of USS and LFTs in diagnosing choledocholithiasis. Five studies included in total. • All five studies included examined accuracy of USS with 523 participants in total. • Only one study included compared the accuracy of LFTs (specifically ALP and bilirubin) and USS in the same population (N=262). • Positive test reference standard for all studies involved either the surgical or endoscopic extraction of choledocholithiasis. • Negative test standards involved either a negative surgical/endoscopic	• Cumulative sensitivity for USS 0.73 (95% CI 0.44 - 0.90). • Cumulative specificity for USS 0.91 (95% CI 0.84 - 0.95). • Single study looking at the accuracy of LFTs: - Bilirubin at a cut-off of greater than 22.23 µmol/L; sensitivity of 0.84 (95% CI 0.65 to 0.94), specificity of 0.91 (0.86 to 0.94). - Bilirubin at a cut-off of greater than twice the normal limit; sensitivity of 0.42 (95% CI 0.22 to 0.63) and specificity of 0.97 (95% CI 0.95 to 0.99). - ALP at a cut-off of greater than 125 IU/L; sensitivity of 0.92 (95% CI 0.74 to	• Persistent symptoms with negative USS or normal LFTs may need further investigation with non-invasive tests due to the possibility of false negative results. • Further non-invasive investigations are suggested with abnormal USS or deranged LFT parameters to confirm choledocholithiasis due to the possibility of false positive results. • Results of the review were based on a few studies of

	exploration of the CBD or symptom free follow up for a period of 6 months or greater.	0.99) and specificity of 0.79 (95% CI 0.74 to 0.84). - ALP at a cut-off of greater than twice the normal limit; sensitivity of 0.38 (95% CI 0.19 to 0.59) and specificity of 0.97 (95% CI 0.95 to 0.99).	poor methodological quality and that results should be interpreted with caution.
Boys et al (2014)[11]	• Retrospective review of patients admitted with acute Cholecystitis between 2007 and 2011. • CBD diameter on USS was analysed for patients with and without CBD calculi on pre-operative MRCP/ERCP. • 248 participants included of which 48 were found to have choledocholithiasis.	• Mean CBD diameter was found to be significantly narrower in those patients without choledocholithiasis compared to those with choledocholithiasis; 5.80 VS 7.08 (P=0.0043). • Excluding patients with choledocholithiasis demonstrated on USS, the percentages of patients found to have choledocholithiasis on MRCP/ERCP at varying ranges of CBD diameter were similar; 68.8% in those with CBD diameter <6mm, 69.2% in 6-9.9mm and 85.7% in those >10mm.	• In patients with acute cholecystitis CBD diameter on USS is a poor predictor of choledocholithiasis.
Qui et al (2015)[12]	• Single centre retrospective review of all patients undergoing MRCP over a 3-year period from 2011. • Patients with confirmed CBD calculi on MRCP who had undergone prior imaging with USS were selected for further review (N=109). • Patients were sub-grouped into those with USS findings of choledocholithiasis prior to MRCP and those without. • 11 indicators analysed, including LFT parameters and USS findings in both	• The detection rate for choledocholithiasis on USS (using MRCP as a reference standard) was found to be 55.05%. • ALT levels and concurrent acute cholecystitis were found to be negatively associated with an USS diagnosis choledocholithiasis (P=0.038 and P=0.001 respectively), whereas CBD diameter was shown to have a positive correlation (P=0.000).	• Use of USS in the pre-operative screening of patients for choledocholithiasis is unreliable. • Authors suggested the routine use of MRCP for the screening of choledocholithiasis could be feasible where MRCP is readily available and costs are favourable.

	groups.		
Ahn et al (2016) [10]	• Single centre retrospective review of patients with gallbladder related symptoms seen in the emergency room between 2004 and 2009. • Patients were divided into three groups: acute cholecystitis with no choledocholithiasis (AC-CBD, N=556), acute cholecystitis with choledocholithiasis detected either with ERCP or surgery (AC +CBD, N=98) and chronic cholecystitis with no choledocholithiasis (CC-CBD, N=200). • LFT parameters at admission and repeat LFT parameters over a period of time were analysed.	• Mean LFT parameters at admission for the AC + CBD group were significantly elevated compared to AC – CBD and CC – CBD groups (P<0.001). • Repeat LFT parameters at a mean follow up of 4 days decreased significantly in the AC – CBD group whereas parameters remained unchanged (except for ALP), in the AC + CBD group at a mean follow up of 4.3 days. • GGT was found to be the most reliable predictor of CBD calculi at an optimal cut off of 224 IU/L (sensitivity 80.6 %, specificity 75.3 %, P<0.001).	• Derangement of LFT parameters can be used as a predictor of concurrent choledocholithiasis in patients with acute cholecystitis. • Identification of patients with on-going derangement of LFT parameters associated with choledocholithiasis allows for selective further diagnostic testing in this cohort. • GGT was shown to have the highest predictability for concurrent choledocholithiasis in acute cholecystitis.
Rubin et al (2013)[13]	• Retrospective review of ERCP's performed between 2007 and 2010. • 1080 ERCP procedures performed of which 521 were due to suspected choledocholithiasis. • Data for predictors of choledocholithiasis as defined by ASGE classification were analysed for patients.	• Choledocholithiasis was found in 56% of patients undergoing ERCP (N=293). • Choledocholithiasis on USS, bilirubin levels >4mg/dl and a dilated CBD on USS were all shown to be independently associated with CBD calculi on ERCP (P=<0.05) with the highest odds ratio demonstrated for CBD calculi on USS (OR 5.40, 95% CI 2.04 – 14.30, P=0.00179). • Sensitivities and specificities for each of the predictors when used individually	• Use of the ASGE classification allows accurate risk stratification of patients with suspected CBD calculi. • Authors concluded, "the sensitivity and specificity of the current predictors are too low to obviate the need for non-invasive tests (EUS/MRCP) to confirm

		were poor with the presence of CBD calculi on ERCP.	the presence of choledocholithiasis in all risk groups".
Magalhães et al (2014)[14]	• Single centre retrospective review of all patients undergoing ERCP for suspected CBD calculi over a 4 year period (N=268). • Data for predictors of choledocholithiasis as defined by ASGE classification were analysed for patients.	• Choledocholithiasis were present in 66.8% of patients who underwent ERCP (N=179). • Apart from gallstone pancreatitis, all other predictors had a statistically significant association with choledocholithiasis on ERCP with the highest odds ratio found for choledocholithiasis shown on USS (OR 11.25, 95% CI 5.32 – 23.81, P=<0.001). • Sensitivity for bilirubin >4mg/dl and CBD calculi shown on USS found to be 89.9% and 70.8% respectively. • High sensitivity (86.0%) and PPV (79.8%) for choledocholithiasis on ERCP demonstrated for patients stratified into the high risk category. However a poor specificity (56.2%) was demonstrated	• The use of predictors of choledocholithiasis as defined by ASGE classification allows accurate risk stratification of patients with suspected choledocholithiasis . • A low overall specificity using the ASGE predictors was demonstrated. Of particular concern was the low specificity found in the high risk group (56.2%) with a risk of patients undergoing unnecessary subsequent ERCP procedures (as recommended by ASGE guidelines) without further testing with non-invasive modalities such as MRCP and EUS.
Narváez-Rivera et al (2016)[16]	• Single centre prospective review of all patients admitted with suspected choledocholithiasis over a 2 year period (2012-2014). • Patients who met the ASGE classification for intermediate (N=48)	• In high risk patients the accuracy for choledocholithiasis using the ASGE predictors was 59% (sensitivity 85.5%, specificity 24.3%). • In intermediate risk patients the accuracy was 41% (sensitivity 14.4%, specificity	• Authors concluded that the accuracy of the ASGE predictors in intermediate and high risk groups were inadequate with 111 patients (43%) undergoing

	and high risk probability of choledocholithiasis (N=208) were selected for further review. • All patients underwent ERCP with a positive procedure defined as the presence of CBD calculi or sludge.	75.6%). • No statistically significant difference was found in the detection rate between the two groups (P=0.053).	unnecessary ERCP procedures in the study population. • Authors recommended confirmatory imaging using MRCP or EUS prior to ERCP in intermediate/high risk groups in the absence of ascending cholangitis.

Table 2: Summary of studies examining serological predictors and ultrasonography in patients with suspected choledocholithiasis.

Article	Study Design	Results	Conclusions
Giljaca et al (2015)[7]	• Cochrane systematic review comparing the accuracy of EUS and MRCP in diagnosing choledocholithiasis. • Eighteen studies included in total (11 looking at EUS only, 5 looking at MRCP only and 2 comparing both). • Total number of 2366 participants of whom 976 had choledocholithiasis demonstrated. • In all studies, presence of choledocholithiasis confirmed with endoscopic or surgical extraction. Negative test standard involved either a negative endoscopic/surgical exploration of the CBD or symptom free follow up for 6 months or greater.	• The use of EUS was evaluated in 1537 patients of whom 686 were found to have choledocholithiasis. • Sensitivities for EUS ranged from 0.75 – 1.00 with a summary sensitivity of 0.95 (95% CI 0.91 – 0.97). Specificities for EUS ranged from 0.85 – 1.00 with a summary specificity of 0.97 (95% CI 0.94 – 0.99). • The use of MRCP was evaluated in 996 patients of whom 361 were found to have choledocholithiasis. • Sensitivities for MRCP ranged from 0.77 – 1.00 with a summary sensitivity of 0.93 (95% CI 0.87 – 0.96). Specificities for MRCP ranged from 0.73 – 0.99 with a summary specificity of 0.96 (95% CI 0.90 – 0.98). • There was no significant difference found in the sensitivity or specificity between EUS and MRCP (P=0.5).	• Both EUS and MRCP were found to have high diagnostic accuracy for the detection of choledocholithiasis. • Patients with positive EUS or MRCP findings should undergo either endoscopic or surgical CBD clearance. • Patients with negative EUS or MRCP procedures do not need further invasive investigations. • Patients with negative EUS or MRCP procedures should undergo further investigations if symptoms persist. • Authors commented that studies were of poor methodological quality therefore results should be interpreted with caution.
Prachayakul et al (2014)[15]	• Single centre retrospective review of patients undergoing EUS between 2009 and 2012 for clinically suggestive	• 29/93 had choledocholithiasis on EUS. • 33/93 patients underwent ERCP on the same day as their EUS. 28/29 patients with	• EUS was found to be an accurate diagnostic tool for choledocholithiasis and

	choledocholithiasis in who initial imaging examinations were inconclusive (N=93). • Patients were subdivided into intermediate (52.7% of patients) and high likelihood groups (47.3% of patients) based on the predictors of choledocholithiasis as defined by the ASGE classification. • 60/93 patients underwent no further intervention following negative EUS procedures. These patients were followed up for a minimum of 6 months.	positive EUS had choledocholithiasis on ERCP (one false positive EUS result). Remaining 4 patients all had negative ERCP procedures (true negative EUS). • Of the 60 patients who underwent no further intervention 36.6% (N=34) were lost to follow up within 6 months (all patients lost to follow up were contacted by telephone and had either remained asymptomatic or underwent ERCP at another institution, no further data given in study). • Sensitivity of EUS found to be 100%, PPV 96.55%, NPV 100% and specificity 80%. • Choledocholithiasis were found in 24.44% of patients in the intermediate risk group and 38.63% of patients in the high risk group.	its use may limit the number of unnecessary ERCP procedures. • Authors commented that the use of clinical criteria as defined by the ASGE classification may not provide accurate prediction of the presence of choledocholithiasis as demonstrated by the low percentages of patients with choledocholithiasis in the intermediate and high risk groups.
Anand et al (2015)[17]	• Single centre retrospective review of patients undergoing ERCP for choledocholithiasis. All patients included were defined as high risk for choledocholithiasis (based on the ASGE classification). • Patients were divided into those undergoing ERCP only (N=176) and those who underwent MRCP prior to ERCP (N=48).	• Patients in the MRCP group were found to have statistically significant longer waiting times to ERCP procedures, greater radiology charges and longer inpatient stays. • Choledocholithiasis were demonstrated in 26/48 patients undergoing MRCP (54%) with a further 2 patients shown to have CBD strictures. 20/48 patients had normal MRCP procedures (42%). • In those with normal MRCP procedures choledocholithiasis were demonstrated on	• Authors commented that the use of MRCP in high risk groups is associated with longer inpatient stays and higher costs without a significant influence on patient or procedural outcomes.

		ERCP in 5 patients (25%) with a further 4 patients found to have CBD sludge (20%).	
Gurusamy et al(2015)[18]	• Cochrane systematic review comparing the accuracy of ERCP and IOC in diagnosing choledocholithiasis. • Ten studies were included in total. Five studies looked at ERCP with a total of 318 participants, of which 180 were found to have choledocholithiasis. Five studies looked at IOC with a total of 654 participants, of which 125 were found to have choledocholithiasis. • The endoscopic or surgical extraction of choledocholithiasis was used as a positive test standard. Negative test standard involved either a negative endoscopic/surgical exploration of the CBD or symptom free follow up for 6 months or greater.	• ERCP sensitivity was 0.67 – 0.94 with cumulative sensitivity of 0.83 (95% CI 0.72 – 0.90). Specificities for ERCP ranged from 0.92 – 1.00 with a summary specificity of 0.99 (95% CI 0.94 – 1.00). • Sensitivities for IOC ranged from 0.75 – 1.00 with a summary sensitivity of 0.99 (95% CI 0.83 – 1.00). Specificities for EUS ranged from 0.96 – 1.00 with a summary specificity of 0.99 (95% CI 0.95 – 1.00). • There was weak evidence demonstrated favouring the sensitivity of IOC over ERCP in diagnosing CBD calculi (P=0.05). • There was no difference found in the specificity of both tests (p=0.7).	• There was some weak evidence supporting a higher sensitivity of IOC over ERCP in diagnosing choledocholithiasis. However, authors commented that this finding may be unreliable as both tests were not conducted in the same study population and most of the studies included were methodologically flawed. • As both tests have similar accuracy in diagnosing CBD calculi the choice of test will likely be guided by surgeon preference for further management (i.e. CBD exploration following positive IOC or therapeutic ERCP following a positive diagnostic ERCP).

Table 3: Summary of studies examining further diagnostic tests following initial screening in patients with suspected choledocholithiasis.

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