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[Diagnostic Test Accuracy Review]

Endoscopic ultrasound versus magnetic resonance cholangiopancreatography for common bile duct stones

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ABSTRACT

Background

Endoscopic ultrasound (EUS) and magnetic resonance cholangiopancreatography (MRCP) are tests used in the diagnosis of common bile duct stones in patients suspected of having common bile duct stones prior to undergoing invasive treatment. There has been no systematic review of the accuracy of EUS and MRCP in the diagnosis of common bile duct stones using appropriate reference standards.

Objectives

To determine and compare the accuracy of EUS and MRCP for the diagnosis of common bile duct stones.

Search methods

We searched MEDLINE, EMBASE, Science Citation Index Expanded, BIOSIS, and Clinicaltrials.gov until September 2012. We searched the references of included studies to identify further studies and of systematic reviews identified from various databases (Database of Abstracts of Reviews of Effects (DARE), Health Technology Assessment (HTA), Medion, and ARIF (Aggressive Research Intelligence Facility)). We did not restrict studies based on language or publication status, or whether data were collected prospectively or retrospectively.

Selection criteria

We included studies that provided the number of true positives, false positives, false negatives, and true negatives for EUS or MRCP. We only accepted studies that confirmed the presence of common bile duct stones by extraction of the stones (irrespective of whether this was done by surgical or endoscopic methods) for a positive test, and absence of common bile duct stones by surgical or endoscopic negative exploration of the common bile duct or symptom free follow-up for at least six months for a negative test, as the reference standard in people suspected of having common bile duct stones. We included participants with or without prior diagnosis of cholelithiasis; with or without symptoms and complications of common bile duct stones, with or without prior treatment for common bile duct stones; and before or after cholecystectomy. At least two authors independently screened abstracts and selected studies for inclusion.

Data collection and analysis

Two authors independently collected the data from each study. We used the bivariate model to obtain pooled estimates of sensitivity and specificity.

Main results

We included a total of 18 studies involving 2366 participants (976 participants with common bile duct stones and 1390 participants without common bile duct stones). Eleven studies evaluated EUS alone, and five studies evaluated MRCP alone. Two studies evaluated both tests. Most studies included patients who were suspected of having common bile duct stones based on abnormal liver function tests; abnormal transabdominal ultrasound; symptoms such as obstructive jaundice, cholangitis, or pancreatitis; or a combination of the above. The proportion of participants who had undergone cholecystectomy varied across studies. Not one of the studies was of high methodological quality. For EUS, the sensitivities ranged between 0.75 and 1.00 and the specificities ranged between 0.85 and 1.00. The summary sensitivity (95% confidence interval (CI)) and specificity (95% CI) of the 13 studies that evaluated EUS (1537 participants; 686 cases and 851 participants without common bile duct stones) were 0.95 (95% CI 0.91 to 0.97) and 0.97 (95% CI 0.94 to 0.99). For MRCP, the sensitivities ranged between 0.77 and 1.00 and the specificities ranged between 0.73 and 0.99. The summary sensitivity and specificity of the seven studies that evaluated MRCP (996 participants; 361 cases and 635 participants without common bile duct stones) were 0.93 (95% CI 0.87 to 0.96) and 0.96 (95% CI 0.90 to 0.98). There was no evidence of a difference in sensitivity or specificity between EUS and MRCP (P value = 0.5). From the included studies, at the median pre-test probability of common bile duct stones of 41% the post-test probabilities (with 95% CI) associated with positive and negative EUS test results were 0.96 (95% CI 0.92 to 0.98) and 0.03 (95% CI 0.02 to 0.06). At the same pre-test probability, the post-test probabilities associated with positive and negative MRCP test results were 0.94 (95% CI 0.87 to 0.97) and 0.05 (95% CI 0.03 to 0.09).

Authors' conclusions

Both EUS and MRCP have high diagnostic accuracy for detection of common bile duct stones. People with positive EUS or MRCP should undergo endoscopic or surgical extraction of common bile duct stones and those with negative EUS or MRCP do not need further invasive tests. However, if the symptoms persist, further investigations will be indicated. The two tests are similar in terms of diagnostic accuracy and the choice of which test to use will be informed by availability and contra-indications to each test. However, it should be noted that the results are based on studies of poor methodological quality and so the results should be interpreted with caution. Further studies that are of high methodological quality are necessary to determine the diagnostic accuracy of EUS and MRCP for the diagnosis of common bile duct stones.

PLAIN LANGUAGE SUMMARY

Endoscopic ultrasound versus magnetic resonance cholangiopancreatography for the diagnosis of common bile duct stones

Background

Bile, produced in the liver and stored temporarily in the gallbladder, is released into the small bowel on eating fatty food. The common bile duct (CBD) is the tube through which bile flows from the gallbladder to the small bowel. Stones in the CBD (CBD stones) are usually formed in the gallbladder before migration into the bile duct. They can obstruct the flow of bile leading to jaundice (yellowish discolouration of skin, whites of the eyes, and dark urine), infection of the bile (cholangitis), and inflammation of the pancreas (pancreatitis), which can be life threatening. Various diagnostic tests can be performed for the diagnosis of CBD stones. Depending upon the availability of resources, these stones are removed endoscopically (usually the case) or may be removed as part of the operation performed to remove the gallbladder (it is important to remove the gallbladder since the stones continue to form in the gallbladder and can cause recurrent problems). Prior to removal, invasive tests such as endoscopic retrograde cholangiopancreatography (ERCP) or intraoperative cholangiography (IOC) can be performed to detect CBD stones. However, before performing such invasive tests to diagnose CBD stones, non-invasive tests such as endoscopic ultrasound (EUS) (using ultrasound attached to the endoscope) and magnetic resonance cholangiopancreatography (MRCP) are used to identify people at high risk of having CBD stones so that only those at high risk can be subjected to further tests.

Study characteristics

We performed a thorough search for studies that reported the accuracy of EUS or MRCP in the diagnosis of CBD stones. We included a total of 18 studies involving 2532 participants. Eleven studies evaluated EUS alone, five studies evaluated MRCP alone, and two studies evaluated both tests. A total of 1537 participants were included in the 13 studies that evaluated EUS and 995 participants were included in the seven studies that evaluated MRCP. Most studies included patients who were suspected of having CBD stones based on abnormal blood tests, abnormal ultrasound, or symptoms such as jaundice or pancreatitis, or a combination of the above. The proportion of participants who had undergone previous gallbladder removal varied across studies.

Key results

Based on an average sensitivity of 95% for EUS, on average 95 out of 100 people with CBD stones will be detected while the remaining 5 people will be missed and will not receive appropriate treatment. The average number of people with CBD stones detected using EUS may vary between 91 and 97 out of 100 people. The average specificity of 97% for EUS means that on average 97 out of 100 people without CBD stones will be identified as not having CBD stones; 3 out of 100 would be false positives and would not receive appropriate treatment. The average number of false positives could vary between 1 and 6 out of 100 people. For MRCP, an average sensitivity of 93% means that on average 93 out of 100 people with CBD stones will be detected while the remaining 7 people will be missed and will not receive appropriate treatment. The average number of people with CBD stones detected using MRCP may vary between 87 and 96 out of 100 people. With an

average specificity of 96% for MRCP, 96 out of 100 people without CBD stones will be identified as not having CBD stones; 4 out of 100 would be false positives and would not receive appropriate treatment. The average number of false positives could vary between 2 and 10 out of 100 people. This means that some people with CBD stones can be missed by EUS and MRCP. Although most people with a negative EUS or MRCP do not need to undergo further invasive tests, in the presence of persistent symptoms further testing with MRCP if the patient had undergone EUS or EUS if the patient had undergone MRCP, ERCP, or IOC may be indicated. There is little to choose between EUS and MRCP in terms of diagnostic accuracy.

Quality of evidence

All the studies were of low methodological quality, which may undermine the validity of our findings.

Future research

Further studies of high methodological quality are necessary.

SUMMARY OF FINDINGS

Summary of findings 1. Performance of endoscopic ultrasound and magnetic resonance cholangiopancreatography for diagnosis of common bile stones

Population	Patients suspected of having common bile duct stones based on symptoms, liver function tests, and ultrasound				
Settings	Secondary and tertiary care setting in different parts of the world				
Index tests	Endoscopic ultrasound (EUS) and magnetic resonance cholangiopancreatography (MRCP)				
Reference standard	Endoscopic or surgical extraction of stones in patients with a positive index test result or clinical follow-up (minimum 6 months) in patients with a negative index test result				
Target condition	Common bile duct stones				
Number of studies	A total of 18 studies were included. Thirteen studies (686 cases, 1537 participants) evaluated EUS and 7 studies (361 cases, 996 participants) evaluated MRCP. Two of the studies evaluated both tests in the same patients				
Methodological quality concerns	All the studies were of poor methodological quality; most studies were at high risk of bias or gave high concern about applicability across all domains of quality assessment, or both				
Pre-test probability¹	Test	Summary sensitivity (95% CI)	Summary specificity (95% CI)	Positive post-test probability (95% CI)²	Negative post-test probability (95% CI)³
0.14	EUS	0.95 (0.91 to 0.97)	0.97 (0.94 to 0.99)	0.85 (0.72 to 0.93)	0.01 (0.01 to 0.02)
	MRCP	0.93 (0.87 to 0.96)	0.96 (0.89 to 0.98)	0.79 (0.61 to 0.90)	0.01 (0.01 to 0.02)
0.30	EUS	0.95 (0.91 to 0.97)	0.97 (0.94 to 0.99)	0.94 (0.87 to 0.97)	0.02 (0.01, 0.04)
	MRCP	0.93 (0.87 to 0.96)	0.96 (0.89 to 0.98)	0.90 (0.80 to 0.96)	0.03 (0.02, 0.06)
0.41	EUS	0.95 (0.91 to 0.97)	0.97 (0.94 to 0.99)	0.96 (0.92 to 0.98)	0.03 (0.02, 0.06)
	MRCP	0.93 (0.87 to 0.96)	0.96 (0.89 to 0.98)	0.94 (0.87 to 0.97)	0.05 (0.03 to 0.09)
0.48	EUS	0.95 (0.91 to 0.97)	0.97 (0.94 to 0.99)	0.97 (0.93, 0.99)	0.05 (0.03 to 0.08)
	MRCP	0.93 (0.87 to 0.96)	0.96 (0.89 to 0.98)	0.95 (0.90 to 0.98)	0.06 (0.04 to 0.11)
0.68	EUS	0.95 (0.91 to 0.97)	0.97 (0.94 to 0.99)	0.99 (0.97 to 0.99)	0.10 (0.06 to 0.16)

MRCP	0.93 (0.87 to 0.96)	0.96 (0.89 to 0.98)	0.98 (0.95 to 0.99)	0.13 (0.08 to 0.23)
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Comparison of the diagnostic accuracy of EUS and MRCP: at pre-test probabilities of 14%, 41%, and 68%, out of 100 people with positive EUS, common bile duct stones will be present in 85, 96, and 99 people respectively; while out of 100 people with positive MRCP, common bile duct stones will be present in 79, 94, and 98 people. For the same pre-test probabilities, out of 100 people with negative EUS, common bile duct stones will be present in 1, 3, and 10 people respectively; while out of 100 people with negative MRCP, common bile duct stones will be present in 1, 5, and 13 people respectively.

Conclusions: the performance of EUS and MRCP appears to be comparable for diagnosis of common bile duct stones. The strength of the evidence for the test comparison was weak because the studies were methodologically flawed, and only two studies made head-to-head comparisons of EUS and MRCP.

¹ The pre-test probability (proportion with common bile duct stones out of the total number of participants) was computed for each included study. These numbers represent the minimum, lower quartile, median, upper quartile and the maximum values from the 18 studies.

² Post-test probability of common bile duct stones in people with positive index test results.

³ Post-test probability of common bile duct stones in people with negative index test results.

BACKGROUND

Biliary stones are conglomerates of precipitated bile salts that form in the gallbladder or the common bile duct. The common bile duct carries bile from the liver to the duodenum (first part of the small intestine). The term 'gallstones' generally refers to the stones in the gallbladder while the term 'common bile duct stones' refers to stones in the common bile duct. Common bile duct stones may form inside the common bile duct (primary common bile duct stones), or they may form in the gallbladder and migrate to the common bile duct (secondary common bile duct stones) (Williams 2008). A significant proportion of patients presenting with common bile duct stones may be asymptomatic (Sarli 2000). In some patients the stones pass silently into the duodenum, and in others the stones cause clinical symptoms like biliary colic, jaundice, cholangitis, or pancreatitis (Caddy 2006). The prevalence of gallstone disease in the general population is about 6% to 15%, with a higher prevalence in females (Barbara 1987; Loria 1994). Only 2% to 4% of people with gallstones become symptomatic with biliary colic (pain), acute cholecystitis (inflammation), obstructive jaundice, or gallstone pancreatitis in a year (Attili 1995; Haldestam 2004), and removal of the gallbladder is recommended in people with symptomatic gallstones (Gurusamy 2010). Among patients who undergo laparoscopic cholecystectomy (removal of the gallbladder) for symptomatic gallstones, 3% to 22% of patients also have concomitant common bile duct stones (Arnold 1970; Lill 2010; Yousefpour Azary 2011).

Common bile duct stones present in multiple ways. Central and right sided upper abdominal pain is a common presentation (Anciaux 1986; Roston 1997). Jaundice, caused by an impacted stone in the common bile duct leading to obstruction of bile passage into the duodenum, is another presentation. It may subsequently resolve if the common bile duct stone passes spontaneously into the duodenum. This happens in 54% to 73% of patients with common bile duct stones in whom cholecystectomy is performed for gallstones (Tranter 2003; Lefemine 2011). Another, more dangerous, complication of common bile duct stones is acute cholangitis. Cholangitis is clinically defined by Charcot's triad which includes elevated body temperature, pain under the right ribcage, and jaundice (Raraty 1998; Salek 2009). Acute cholangitis is caused by an ascending bacterial infection of the common bile duct and the biliary tree along with biliary obstruction. This complication is present in 2% to 9% of patients admitted for gallstone disease (Saik 1975; Tranter 2003) and a mortality of approximately 24% is recorded (Salek 2009). Common bile duct stones may also cause acute pancreatitis, accounting for 33% to 50% of all patients with acute pancreatitis (Corfield 1985; Toh 2000). Acute pancreatitis is usually a self-limiting disease and is generally sufficiently treated by conservative measures in its mild form (Neoptolemos 1988). However, a more severe pancreatitis may evolve in approximately 27% to 37% of patients with common bile duct stone induced pancreatitis, with mortality around 6% to 9% (Mann 1994; Toh 2000).

Suspicion of common bile duct stones can be investigated by laboratory liver function tests (Barkun 1994) or imaging tests like abdominal ultrasound (Ripolles 2009). Further testing may include endoscopic ultrasound (EUS) (Aljebreen 2008), magnetic resonance cholangiopancreatography (MRCP) (Stiris 2000), endoscopic retrograde cholangiopancreatography (ERCP) (Geron 1999), and intraoperative cholangiography (IOC) (Fiore

1997). Currently, these are the recommended tests for diagnosis of common bile duct stones. Of these tests, IOC can only be done during an operation as the test requires surgical cannulation of the common bile duct during cholecystectomy. The other tests may be used before or after cholecystectomy. Usually the first diagnostic tests that most patients undergo are liver function tests and abdominal ultrasound. Invasive diagnostic tests are usually reserved for patients with suspected common bile duct stones based on non-invasive diagnostic tests, or when therapeutic measures are necessary (Freitas 2006).

Conventional computed tomogram (CT scan), CT cholangiogram, laparoscopic ultrasound, and ERCP guided intraductal ultrasound are of limited use for diagnosing common bile duct stones (Maple 2010).

Target condition being diagnosed

Common bile duct stones. We did not differentiate the target condition with respect to common bile duct stone size, degree of common bile duct obstruction, and the presence or absence of symptoms.

Index test(s)

MRCP uses a high magnetic field to cause fluctuations of tissues at a molecular level. These minute fluctuations are then registered by the receiver as differences in frequencies of fluctuation for the different types of tissues. This information is then combined using computer software to generate high-resolution pictures of the scanned area. A common bile duct stone is seen as a hypointense round or oval area of low signal in the hyperintense common bile duct (Stiris 2000; RadiologyInfo 2011).

Endoscopic ultrasound combines endoscopy (a flexible tube used to visualise the food-pipe and stomach) with ultrasound. A forward-viewing or side-viewing endoscope with an ultrasound transducer is introduced in the duodenum by visual control, and then high-frequency sound waves are used to inspect the tissues that are in the proximity. Seeing a hyperechoic round or oval structure within the common bile duct is considered a positive test (Fickling 2003; Aljebreen 2008).

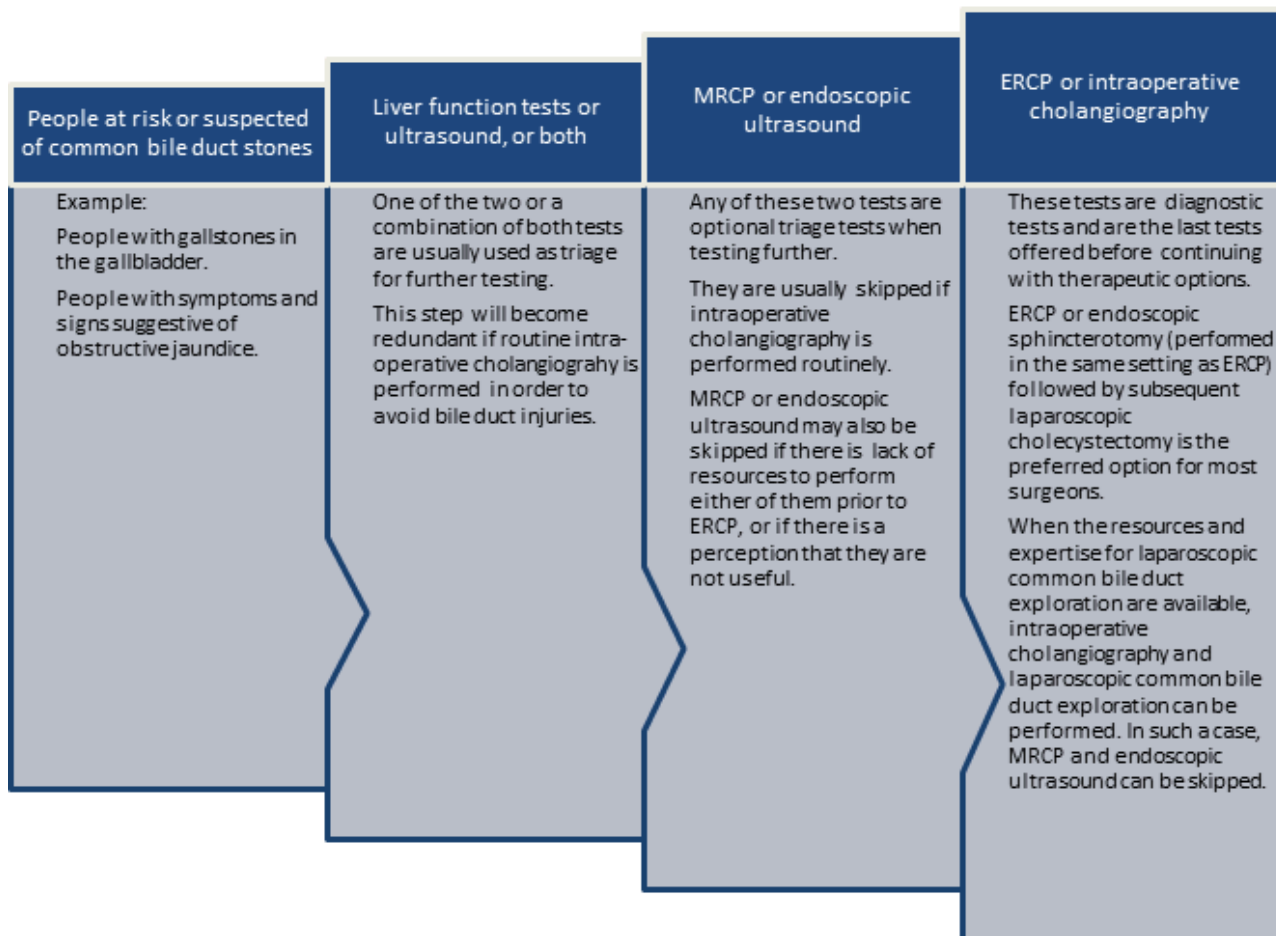
Clinical pathway

Figure 1 illustrates a diagnostic pathway. Patients that are at risk of having common bile duct stones or are suspected of having common bile duct stones (such as patients with gallbladder stones or patients that show symptoms and signs of obstructive jaundice or pancreatitis) will undergo liver function tests and abdominal ultrasound as the first step. An abdominal ultrasound is usually available by the time the person is at risk or is suspected of having common bile duct stones. Usually a combination of both tests is used as triage tests before further testing is done in the second step, but these can be used as the definitive diagnostic tests to carry out a therapeutic option (for example endoscopic or surgical common bile duct exploration) (Williams 2008; ASGE Standards of Practice Committee 2010). MRCP or EUS are tests in the second step of the diagnostic pathway, which are used as optional triage tests prior to tests used in the third step of the diagnostic pathway; but they can also be used as definitive diagnostic tests to carry out a therapeutic option, that is, some people attempt extraction of stones irrespective of the ERCP or IOC findings. MRCP and EUS are not usually combined since the positive or negative

results of one or the other is usually accepted for further clinical decision making, without taking into consideration the results of liver function tests or transabdominal ultrasound, as it is generally believed that MRCP and EUS have better diagnostic accuracy than liver function tests or transabdominal ultrasound. ERCP and IOC are used in the third step of the diagnostic pathway. Both tests are done just before the therapeutic intervention. Therapeutic interventions, such as endoscopic or surgical stone extraction, can then be undertaken during the same session. ERCP is done

before endoscopic sphincterotomy and removal of common bile duct stones using a Dormia basket or balloon during the same endoscopic session (Prat 1996; Maple 2010), and IOC is done before surgical common bile duct exploration and removal of common bile duct stones using surgical instruments during an operation for cholecystectomy (Targarona 2004; Freitas 2006; Chen 2007; Williams 2008; ASGE Standards of Practice Committee 2010; Kelly 2010).

Figure 1. The diagnostic pathway for diagnosis of common bile duct stones. Note that ultrasound is generally performed in all patients at risk or suspected of common bile duct stones. Abbreviations MRCP: magnetic resonance cholangiopancreatography ERCP: endoscopic retrograde cholangiopancreatography



MRCP and EUS can be considered as add-on tests in patients with a positive transabdominal ultrasound or liver function tests. Although most patients can undergo either MRCP or EUS, with the choice between the tests being determined by the preference of the surgeon, EUS is the only add-on test possible in patients with contra-indications to magnetic resonance imaging such as claustrophobic patients and patients with cardiac pacemakers (Magnetic Resonance Imaging 2011) while MRCP is the only add-on test possible in patients with Roux-en-Y gastric anastomosis since EUS cannot reach the desired location (Wilson 2010).

Implications of negative tests

In general, patients with negative tests in one step do not undergo further testing. For example, a person with no suggestion of common bile duct stones on liver function tests and ultrasound will not undergo further testing for common bile duct stones. Similarly, persons having no suggestion of common bile duct stones on MRCP or EUS will not undergo further testing for common bile duct stones, and persons with no suggestion of common bile duct stones on ERCP or IOC will not undergo common bile duct clearance. Individuals with a false negative test result can develop complications of common bile duct stones such as

cholangitis and pancreatitis but the natural history of such patients with negative tests in terms of the frequency with which these complications develop is not known. However, it is generally recommended that common bile duct stones are removed when they are identified because of the serious complications associated with their presence (Williams 2008). Although this practice is not evidence-based, this shows the perception among hepatopancreato biliary surgeons and gastroenterologists that it is important not to miss common bile duct stones.

Prior test(s)

Ultrasound and liver function tests are usually used prior to EUS and MRCP (see Figure 1).

Role of index test(s)

EUS and MRCP are employed as add-on tests in the second step of the diagnostic pathway. If positive, the tests are followed by diagnostic tests in the third step of the diagnostic pathway. If negative, the diagnosis of common bile duct stones is ruled out and further invasive testing is not performed.

Alternative test(s)

There are no alternative tests to EUS and MRCP that are in routine clinical use at the second step of the diagnostic pathway. CT cholangiography and intravenous cholangiography may be used in the second step of the diagnostic pathway but are not used routinely. A small proportion of surgeons use postoperative endoscopic sphincterotomy for management of common bile duct stones. In persons in whom postoperative sphincterotomy is used for management of common bile duct stones, IOC may be considered as an alternative to EUS and MRCP.

Rationale

There are several other benign and malignant conditions that may present in a similar manner to common bile duct stones. Benign (non-cancerous) causes of obstructive jaundice include primary sclerosing cholangitis (Penz-Osterreicher 2011), primary biliary cirrhosis (Hirschfield 2011), chronic pancreatitis (Abdallah 2007), autoimmune pancreatitis (Lin 2008), inflammatory strictures of the common bile duct (Krishna 2008), and strictures of the common bile duct caused by prior instrumentation (Lillemoe 2000; Tang 2011). Malignant (cancerous) causes of obstructive jaundice include cholangiocarcinoma (Siddiqui 2011), cancer of the ampulla of Vater as well as other periampullary cancers (Hamade 2005; Choi 2011; Park 2011), and carcinoma of the pancreas (Singh 1990; Kalady 2004). It is important to differentiate between the causes of obstructive jaundice in order to initiate appropriate treatment. The correct diagnosis of common bile duct stones is an essential contribution to this differentiation.

Common bile duct stones are responsible for a range of complications. Common bile duct stones lead to pancreatitis in about 33% to 50% of the patients who have them (Corfield 1985; Toh 2000) and cause mortality in about 6% to 9% of these patients (Mann 1994; Toh 2000). Acute cholangitis appears in 2% to 9% of patients admitted for gallstone disease, with mortality around 24% (Salek 2009). Therefore, it is important to diagnose common bile duct stones in order to treat patients and prevent such complications.

The preferred option for the treatment of common bile duct stones is currently endoscopic sphincterotomy (ES) with balloon trawling followed by laparoscopic cholecystectomy (Ludwig 2001; Spelsberg 2009). Other options include open cholecystectomy with open common bile duct exploration, laparoscopic cholecystectomy with laparoscopic common bile duct exploration, and laparoscopic cholecystectomy with ES (Hong 2006; Dasari 2013). It has been found that approximately half of patients with jaundice, abnormal liver function tests, and common bile duct dilation on ultrasound do not actually have common bile duct stones (Hoyuela 1999) and, therefore, these patients undergo invasive procedures unnecessarily. Accurate diagnosis of common bile duct stones may avoid unnecessary procedures and the complications associated with these procedures. Invasive tests can result in complications; for example, endoscopic retrograde cholangiopancreatography with endoscopic sphincterotomy (ERCP-ES) can have life-threatening complications such as pancreatitis (Gurusamy 2011). Accurate diagnosis of common bile duct stones using non-invasive tests can avoid these complications.

Currently, there are no Cochrane reviews of studies assessing the accuracy of different tests for diagnosing common bile duct stones. This review is one of three reviews evaluating the diagnostic accuracy of different tests in the diagnosis of common bile duct stones and will help in the development of an evidence-based algorithm for diagnosis of common bile duct stones.

OBJECTIVES

To determine and compare the accuracy of EUS and MRCP for the diagnosis of common bile duct stones.

Secondary objectives

To investigate variation in the diagnostic accuracy of EUS and MRCP according to the following potential sources of heterogeneity.

1. Studies at low risk of bias versus those with unclear or high risk of bias (as assessed by the QUADAS-2) tool (Table 1).
2. Full text publications versus abstracts (this may indicate publication bias if there is an association between the results of the study and the study reaching full publication) (Eloubeidi 2001).
3. Prospective versus retrospective studies.
4. Symptomatic versus asymptomatic common bile duct stones (the presence of symptoms may increase the pre-test probability). Symptomatic patients are defined as patients showing upper right quadrant abdominal pain, jaundice, acute cholangitis or acute pancreatitis (Anciaux 1986; Roston 1997; Raraty 1998; Toh 2000; Tranter 2003).
5. Prevalence of common bile duct stones in each included study. The prevalence of common bile duct stones in the population analysed by each included study may vary and cause heterogeneity. Prevalence may also change with the presence of patients with comorbidities that would predispose them to common bile duct stones such as primary sclerosing cholangitis, Caroli's disease, hypercholesterolaemia, sickle cell anaemia, and sphincter of Oddi dysfunction.
6. Proportion of patients with previous cholecystectomy. Cholecystectomy may cause dilatation of the common bile duct (Benjaminov 2013) and subsequently change the accuracy of the index test, particularly imaging modalities.

7. Proportion of patients with common bile duct strictures (only for index tests that use contrast material, as strictures may prevent contrast material from filling the common bile duct completely and, therefore, change the accuracy of the index test).

METHODS

Criteria for considering studies for this review

Types of studies

We included studies providing cross-sectional information comparing one or more of the index tests against a reference standard in the appropriate patient population (see [Participants](#)). We included studies irrespective of language or publication status, or whether data were collected prospectively or retrospectively. We planned to include comparative studies in which EUS and MRCP were performed in the same study population, either by giving all patients both index tests or by randomly allocating patients to receive MRCP or EUS. We planned to exclude diagnostic case-control studies if there were at least four cross-sectional or comparative studies.

Participants

Patients at risk or suspected of having common bile duct stones with or without prior diagnosis of cholelithiasis; with or without symptoms and complications of common bile duct stones or with or without prior treatment for common bile duct stones; and before or after cholecystectomy.

Index tests

Endoscopic ultrasound (EUS) and magnetic resonance retrograde cholangiopancreatography (MRCP).

Target conditions

Common bile duct stones.

Reference standards

We accepted the following reference standards.

- For test positives, we accepted confirmation of a common bile duct stone by extraction of the stone (irrespective of whether this was done by surgical or endoscopic methods).
- For test negatives, we acknowledged that there was no way of being absolutely sure that there were no common bile duct stones. However, we accepted negative results by surgical or endoscopic negative exploration of the common bile duct, or symptom-free follow-up for at least six months as the reference standard. Surgical or endoscopic exploration is adequate but it is not commonly used in patients with negative index tests because of its invasive nature. Therefore, we accepted follow-up as a less adequate reference test. Negative exploration of the common bile duct is likely to be a better reference standard than follow-up for at least six months since most stones already present in the common bile duct are likely to be identified and extracted in this fashion. Six months is an arbitrary choice but we anticipated that most common bile duct stones will manifest during this period.

Search methods for identification of studies

Electronic searches

We searched MEDLINE via PubMed (January 1946 to September 2012), EMBASE via OvidSP (January 1947 to September 2012), Science Citation Index Expanded via Web of Knowledge (January 1898 to September 2012), BIOSIS via Web of Knowledge (January 1969 to September 2012), and Clinicaltrials.gov (September 2012). The search strategies are shown in [Appendix 1](#). We used a common search strategy for the three reviews of which this review is one. The other two reviews assess the diagnostic accuracy of transabdominal ultrasound, liver function tests, ERCP, and IOC ([Gurusamy 2015a](#); [Gurusamy 2015b](#)). We also identified systematic reviews from the Database of Abstracts of Reviews of Effects (DARE), Health Technology Assessment (HTA), Medion, and ARIF (Aggressive Research Intelligence Facility) databases in order to search their reference lists (please see searching other resources).

Searching other resources

We searched the references of the included studies and systematic reviews related to the topic to identify further studies. We also searched for additional articles related to the included studies by performing the 'related search' function in MEDLINE (PubMed) and EMBASE (OvidSP) and a 'citing reference' search (search the articles which cited the included articles) ([Sampson 2008](#)) in Science Citation Index Expanded and EMBASE (OvidSP).

Data collection and analysis

Selection of studies

Three authors (VG and DH or GP) searched the references independently for identification of relevant studies. We obtained full texts for the references that at least one of the authors considered relevant. Two review authors (VG and DH or GP) assessed the full text articles independently. Any differences in study selection were arbitrated by KG. We selected the studies that met the inclusion criteria for data extraction. We included abstracts if sufficient data to create a 2 x 2 table were provided.

Data extraction and management

Two authors (KG and VG) independently extracted the following data from each included study.

1. First author of report.
2. Year of publication of report.
3. Study design (prospective or retrospective; cross-sectional studies or randomised clinical trials).
4. Inclusion and exclusion criteria for individual studies.
5. Total number of patients.
6. Number of males and females.
7. Mean age of the participants.
8. Tests carried out prior to index test.
9. Index test.
10. Reference standard.
11. Number of true positives, false positives, true negatives, and false negatives.

We sought further information on the diagnostic test accuracy data and assessment of methodological quality (please see [Assessment of methodological quality](#)) from the authors of the studies, if

necessary. We resolved any differences between the review authors by discussion till a consensus was reached. We extracted the data excluding participants with indeterminate results but recorded the number of indeterminates and the reference standard results of the patients with indeterminate results.

Assessment of methodological quality

We adopted the quality assessment of diagnostic accuracy studies assessment tool (QUADAS-2) (Whiting 2006; Whiting 2011) for assessment of the methodological quality of included studies as described in Table 1. We considered studies classified at low risk of bias and low concern regarding applicability to the review question as studies at low risk of bias. Any differences in the methodological quality assessments were resolved by discussion between the review authors until a consensus was reached. We sought further information from study authors in order to accurately assess the methodological quality of the included studies.

Statistical analysis and data synthesis

To visually explore between study variation in the performance of each test, we plotted estimates of sensitivity and specificity from each study on forest plots and in receiver operating characteristic (ROC) space. Because our focus of inference was summary points, we used the bivariate model (Reitsma 2005; Chu 2006) to jointly summarise the sensitivity and specificity of each test. This model accounts for between study variability in estimates of sensitivity and specificity through the inclusion of random effects for the logit sensitivity and logit specificity parameters of the bivariate model.

Using all available studies (that is, an indirect comparison), we compared the diagnostic accuracy of EUS and MRCP by including covariate terms for test type in the bivariate model to estimate differences in the sensitivity and specificity of the two tests. We also allowed the variances of the random effects and their covariance to depend on test type thus allowing the variances to differ between tests. We used likelihood ratio tests to compare the fit of different models, and we also compared the estimates of sensitivity and specificity between models to check the robustness of our assumptions about the variances of the random effects. If studies that evaluated EUS and MRCP in the same study population were available, we planned to also perform a direct head-to-head comparison by limiting the test comparison to such studies. Meta-analyses were performed using the `xtnlogit` command in Stata version 13 (Stata-Corp, College Station, Texas, USA).

We created a table of pre-test probabilities (using the observed median and range of prevalence from the included studies) against post-test probabilities. The post-test probabilities were calculated using these pre-test probabilities and the summary positive and

negative likelihood ratios were derived by using the `Stata _diparm` command and functions of the parameter estimates from the bivariate model that we fitted to estimate the summary sensitivities and specificities.

Investigations of heterogeneity

We visually inspected forest plots of sensitivity and specificity, and summary ROC plots to investigate the potential sources of heterogeneity as stated in the [Secondary objectives](#). Where possible given the number of included studies, we planned to formally explore heterogeneity by adding each potential source of heterogeneity listed above as a covariate in the bivariate model (meta-regression with one covariate at a time).

Sensitivity analyses

Exclusion of participants with uninterpretable results can result in an overestimation of diagnostic test accuracy (Schuetz 2012). In practice, uninterpretable test results will generally be considered as test negatives. Therefore, we planned to perform sensitivity analyses by including uninterpretable test results as test negatives, if sufficient data were available.

Assessment of reporting bias

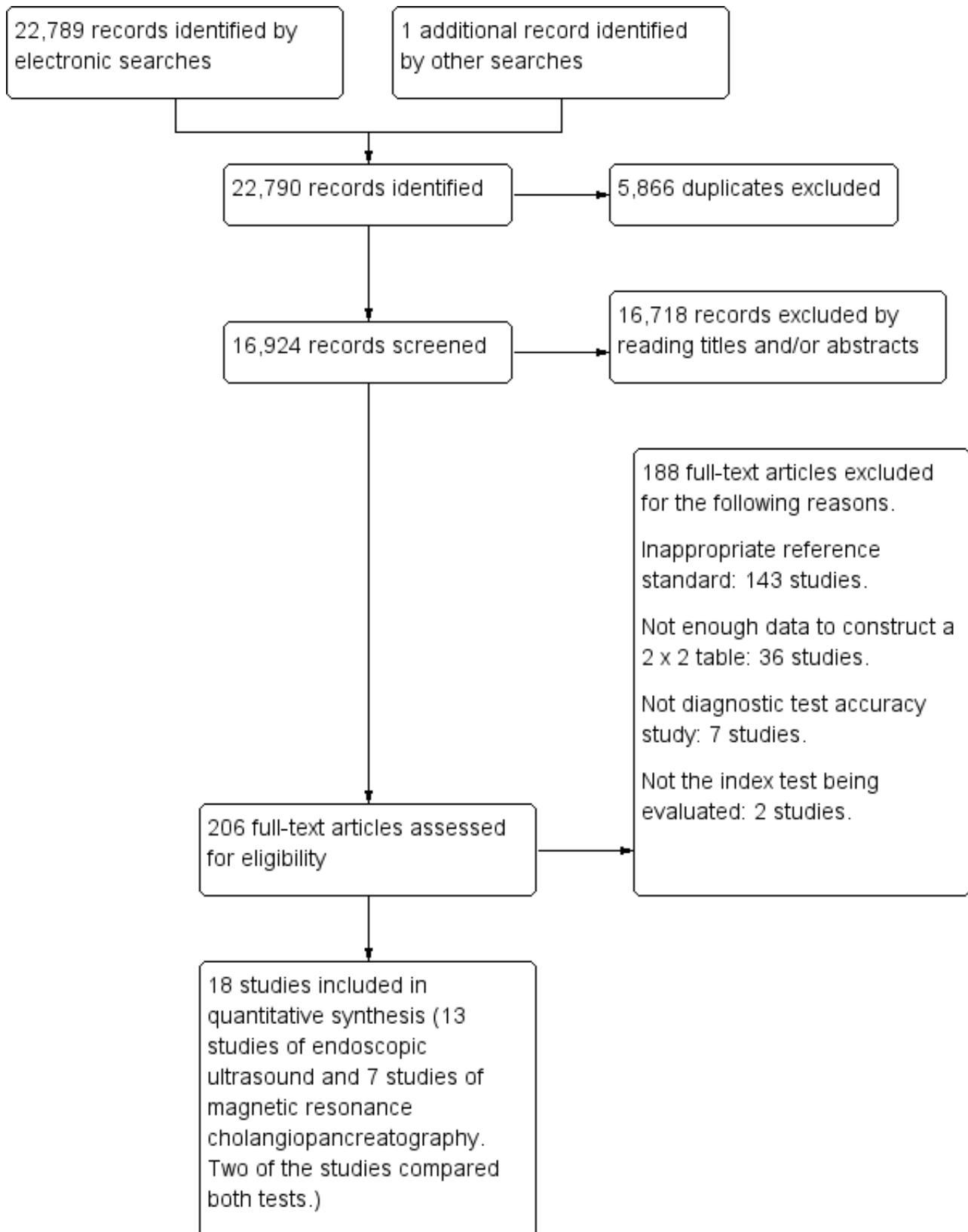
As described in the [Investigations of heterogeneity](#) section, we planned to investigate whether the sensitivity and specificity of the tests differed between studies that were published as full texts and those that were available only as abstracts.

RESULTS

Results of the search

We identified a total of 22,789 references through electronic searches of MEDLINE (n = 8292), EMBASE (n = 10,029), Science Citation Index Expanded and Biosis (n = 4276), and DARE and HTA in the Cochrane Library (n = 192). One additional reference was identified by searching other sources. We excluded 5866 duplicates and 16,718 clearly irrelevant references through reading abstracts. We assessed the remaining 206 references for eligibility by reading the full texts of the publications. We excluded 188 full text articles. The main reasons for exclusion were inappropriate reference standards and lack of data to construct the 2 x 2 tables needed for meta-analyses. The list of excluded studies and reasons for exclusion are listed in the [Characteristics of excluded studies](#) table. We included a total of 18 studies. We were able to obtain additional information from the authors of two of the studies (Prat 1996; Montariol 1998). The flow of studies through the selection process is shown in [Figure 2](#).

Figure 2. Flow of studies through the screening process.



Characteristics of included studies

The characteristics of the included studies are summarised in the [Characteristics of included studies](#) table. We included a total of 18 studies involving 2366 participants in this systematic review. EUS was evaluated by 13 studies involving 1537 participants (686 participants with common bile duct stones and 851 participants without common bile duct stones), and MRCP was evaluated by seven studies involving 996 participants (361 cases and 635 participants without common bile duct stones). The median pre-test probability of common bile duct stones was 0.41, or 41%. The minimum pre-test probability of common bile duct stones in the studies was 0.14, and the maximum pre-test probability was 0.68. Fifteen (Prat 1996; Norton 1997; Canto 1998; Montariol 1998; De Ledinghen 1999; Liu 2001; Boraschi 2002; Jendresen 2002; Kohut 2002; Buscarini 2003; Gautier 2004; Guarise 2005; Ney 2005; Miletic 2006; Fernandez-Esparrach 2007) of the 18 included studies were full text publications. Ten studies (Canto 1998; Montariol 1998; De Ledinghen 1999; Liu 2001; Fazel 2002; Jendresen 2002; Kohut 2002; Buscarini 2003; Gautier 2004; Choo 2012) were prospective studies, one study (Ang 2012) was a retrospective study, and it was unclear whether the remaining studies were prospective or retrospective (Prat 1996; Norton 1997; Boraschi 2002; Guarise 2005; Ney 2005; Miletic 2006; Fernandez-Esparrach 2007). Ten studies (Prat 1996; Norton 1997; Canto 1998; De Ledinghen 1999; Boraschi 2002; Fazel 2002; Kohut 2002; Buscarini 2003; Fernandez-Esparrach 2007; Ang 2012) included patients who were suspected of having common bile duct stones based on abnormal liver function tests; abnormal transabdominal ultrasound; symptoms such as obstructive jaundice, cholangitis, or pancreatitis; or a combination of the above. One study (Liu 2001) included only patients with pancreatitis and another study (Ney 2005) included patients with abnormal liver function tests or ultrasound but excluded those with symptoms. One study (Montariol 1998) excluded patients with abnormal liver function tests, abnormal transabdominal ultrasound, or symptoms; and

one study (Choo 2012) included only patients with a positive intraoperative cholangiogram. Three studies (Gautier 2004; Guarise 2005; Miletic 2006) reported that they performed the test in patients with suspected common bile duct stones but the reasons for suspicion were not stated. The reason for performing the test was not stated in the remaining study (Jendresen 2002). Six studies (Norton 1997; Canto 1998; Montariol 1998; Boraschi 2002; Jendresen 2002; Ney 2005) included participants who had not undergone previous cholecystectomy. In one study (Choo 2012) all the participants had undergone cholecystectomy, while in three studies (Prat 1996; Liu 2001; Buscarini 2003) 8% to 75% of participants had undergone cholecystectomy. The proportion of participants who had undergone cholecystectomy was not stated in the remaining studies. The proportion of patients with common bile duct strictures was not stated in any of the studies.

The criteria for a positive EUS varied between the studies that reported their criteria. While the studies used hyperechoic shadowing inside the common bile duct as the main criterion (Norton 1997; Canto 1998; Montariol 1998; De Ledinghen 1999; Liu 2001; Kohut 2002; Buscarini 2003; Ney 2005; Fernandez-Esparrach 2007), some studies stipulated that these shadows should have acoustic shadowing (Canto 1998; Montariol 1998; Kohut 2002; Ney 2005) and should be mobile (Ney 2005). The criteria for a positive MRCP were signal defects within the common bile duct, defined variably as foci or rounded and oval in some studies (De Ledinghen 1999; Boraschi 2002; Jendresen 2002; Gautier 2004; Guarise 2005; Fernandez-Esparrach 2007).

Methodological quality of included studies

The methodological quality of the included studies is summarised in [Figure 3](#) and [Figure 4](#). Not one of the included studies was of high methodological quality. Regarding applicability concerns, none of the studies were of low concern in all three domains.

Figure 3. Risk of bias and applicability concerns graph: review authors' judgements about each domain presented as percentages across included studies. Each bar shows the number of studies in each category. The index test domain was evaluated separately for each test. Of the 18 included studies, 7 studies evaluated MRCP and 13 studies evaluated EUS; the numbers do not add up to 18 because two of the studies evaluated both tests.

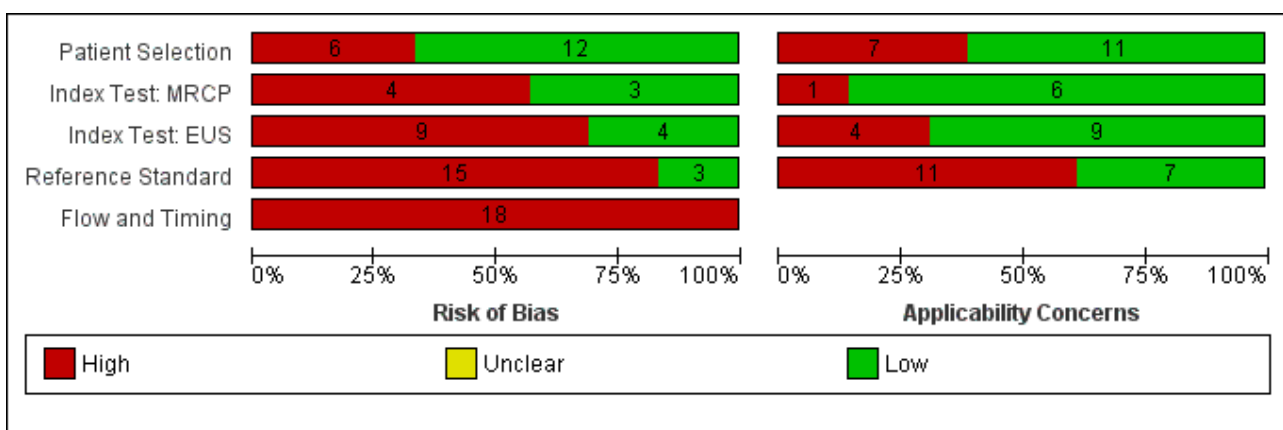


Figure 4. Risk of bias and applicability concerns summary: review authors' judgements about each domain for each included study. In the index test domain, the empty white cell indicates that the study did not evaluate the test.

	Risk of Bias					Applicability Concerns			
	Patient Selection	Index Test: MRCP	Index Test: EUS	Reference Standard	Flow and Timing	Patient Selection	Index Test: MRCP	Index Test: EUS	Reference Standard
Ang 2012	+		-	-	-	+		-	-
Boraschi 2002	-	+		-	-	-	+		+
Buscarini 2003	+		+	-	-	+		+	-
Canto 1998	+		+	-	-	+		+	-
Choo 2012	+		+	+	-	-		-	+
De Ledinghen 1999	-	+	+	-	-	-	+	+	+
Fazel 2002	-		-	-	-	-		-	+
Fernandez-Esparrach 2007	+	-	-	-	-	+	+	+	-
Gautier 2004	+	-		-	-	+	+		-
Guarise 2005	+	-		+	-	+	+		+
Jendresen 2002	+	+		-	-	+	+		-
Kohut 2002	-		-	-	-	-		+	+
Liu 2001	+		-	-	-	+		+	-
Miletic 2006	+	-		-	-	+	-		-
Montariol 1998	+		-	-	-	+		+	-
Ney 2005	+		-	-	-	+		+	-
Norton 1997	-		-	-	-	-		+	-
Prat 1996	-		-	+	-	-		-	+

- High
 ? Unclear
 + Low

Patient selection domain

In the patient selection domain, 12 studies (Canto 1998; Montariol 1998; Liu 2001; Jendresen 2002; Buscarini 2003; Gautier 2004; Guarise 2005; Ney 2005; Miletic 2006; Fernandez-Esparrach 2007; Ang 2012; Choo 2012) had low risk of bias. Eleven studies (Canto 1998; Montariol 1998; Liu 2001; Jendresen 2002; Buscarini 2003; Gautier 2004; Guarise 2005; Ney 2005; Miletic 2006; Fernandez-Esparrach 2007; Ang 2012) had low applicability concerns. The remaining studies were at high risk of bias and were of high concern for applicability because patient recruitment was unclear (Norton 1997; De Ledingham 1999; Boraschi 2002; Fazel 2002; Kohut 2002), participants were excluded inappropriately (Prat 1996), or there were concerns that the participants did not match the types of participants that will undergo these tests in routine clinical practice (Choo 2012).

Index test domain

In the index test domain, seven studies had low risk of bias; four were EUS only studies (Prat 1996; Canto 1998; Buscarini 2003; Choo 2012), two (Boraschi 2002; Jendresen 2002) were MRCP only studies, and one (De Ledingham 1999) evaluated both EUS and MRCP. The remaining studies were at high risk of bias because it was not clear whether the index test results were interpreted without knowledge of the reference standard results. Thirteen studies were of low concern for applicability; seven (Norton 1997; Canto 1998; Montariol 1998; Liu 2001; Kohut 2002; Buscarini 2003; Ney 2005) were EUS only studies, four (Boraschi 2002; Jendresen 2002; Gautier 2004; Guarise 2005) were MRCP only studies, and two (De Ledingham 1999; Fernandez-Esparrach 2007) were studies of both EUS and MRCP. The remaining studies (Prat 1996; Boraschi 2002; Fazel 2002; Gautier 2004; Guarise 2005; Miletic 2006; Ang 2012; Choo 2012) were of high concern for applicability because the criteria for a positive test were not stated.

Reference standard domain

In the reference standard domain, three studies (Prat 1996; Guarise 2005; Choo 2012) had low risk of bias. The remaining studies were at high risk of bias because it was either not clear whether

the reference standards were interpreted without knowledge of the index test results (Norton 1997; Canto 1998; De Ledingham 1999; Liu 2001; Boraschi 2002; Fazel 2002; Kohut 2002; Buscarini 2003; Gautier 2004; Ney 2005; Miletic 2006; Fernandez-Esparrach 2007; Ang 2012) or it was clear that the reference standards were interpreted with the knowledge of the index test results (Montariol 1998; Jendresen 2002). Seven studies (Prat 1996; De Ledingham 1999; Boraschi 2002; Fazel 2002; Kohut 2002; Guarise 2005; Choo 2012) gave low concern about applicability. The remaining 11 studies (Norton 1997; Canto 1998; Montariol 1998; Liu 2001; Jendresen 2002; Buscarini 2003; Gautier 2004; Ney 2005; Miletic 2006; Fernandez-Esparrach 2007; Ang 2012) were of high concern because endoscopic or surgical clearance of the common bile duct was achieved in patients with a positive test and clinical follow-up was performed in patients with a negative test.

Flow and timing domain

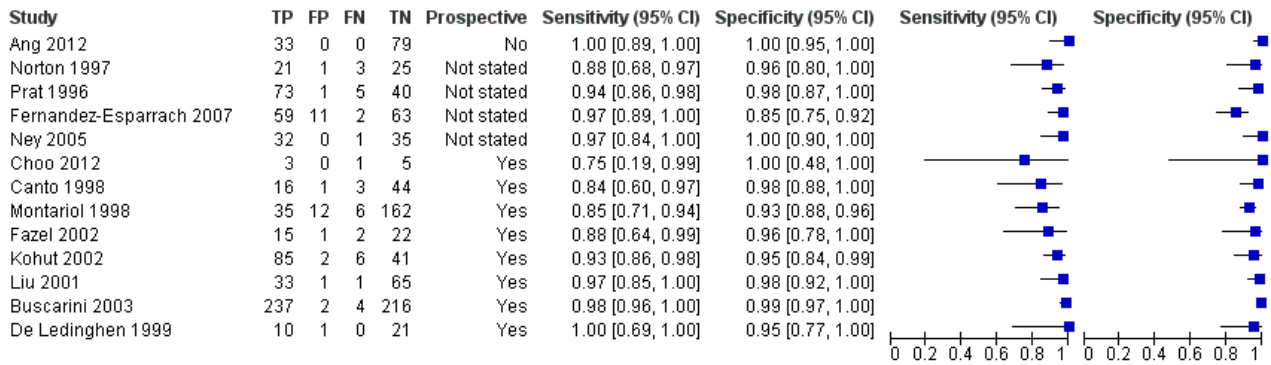
In the flow and timing domain, all 18 studies were at high risk of bias for the following reasons. Six studies (De Ledingham 1999; Boraschi 2002; Fazel 2002; Guarise 2005; Fernandez-Esparrach 2007; Ang 2012) did not report the time interval between the index test and reference standard, and 11 studies (Norton 1997; Canto 1998; Montariol 1998; Liu 2001; Jendresen 2002; Buscarini 2003; Gautier 2004; Ney 2005; Miletic 2006; Fernandez-Esparrach 2007; Ang 2012) did not use the same reference standard since endoscopic or surgical clearance of the common bile duct was achieved in patients with a positive test and clinical follow-up was performed in patients with a negative test. It was not clear whether all the patients were included in the analysis in six studies (Norton 1997; Canto 1998; Fazel 2002; Kohut 2002; Ang 2012; Choo 2012), while some patients were excluded from the analysis in nine studies (Prat 1996; Montariol 1998; De Ledingham 1999; Boraschi 2002; Buscarini 2003; Gautier 2004; Guarise 2005; Miletic 2006; Fernandez-Esparrach 2007).

Findings

The results are summarised in [Summary of findings 1](#), [Figure 5](#), and [Figure 6](#).

Figure 5. Forest plot of endoscopic ultrasound and magnetic resonance cholangiopancreatography for diagnosis of common bile duct stones. The plot shows study specific estimates of sensitivity and specificity (with 95% confidence intervals). The studies are ordered according to study design (prospective or not), sensitivity and study identifier; FN = false negative; FP = false positive; TN = true negative; TP = true positive.

Endoscopic ultrasound



Magnetic resonance cholangiopancreatography

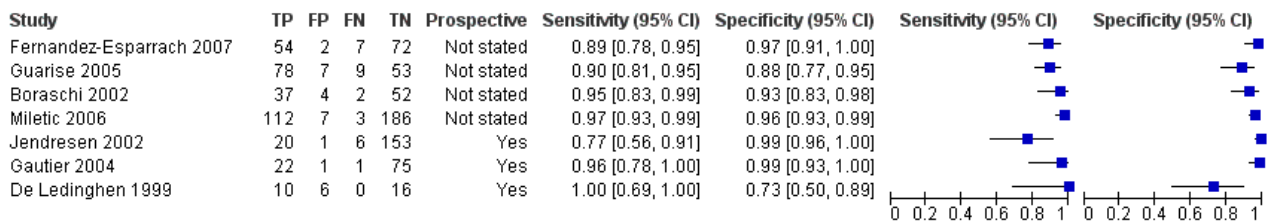
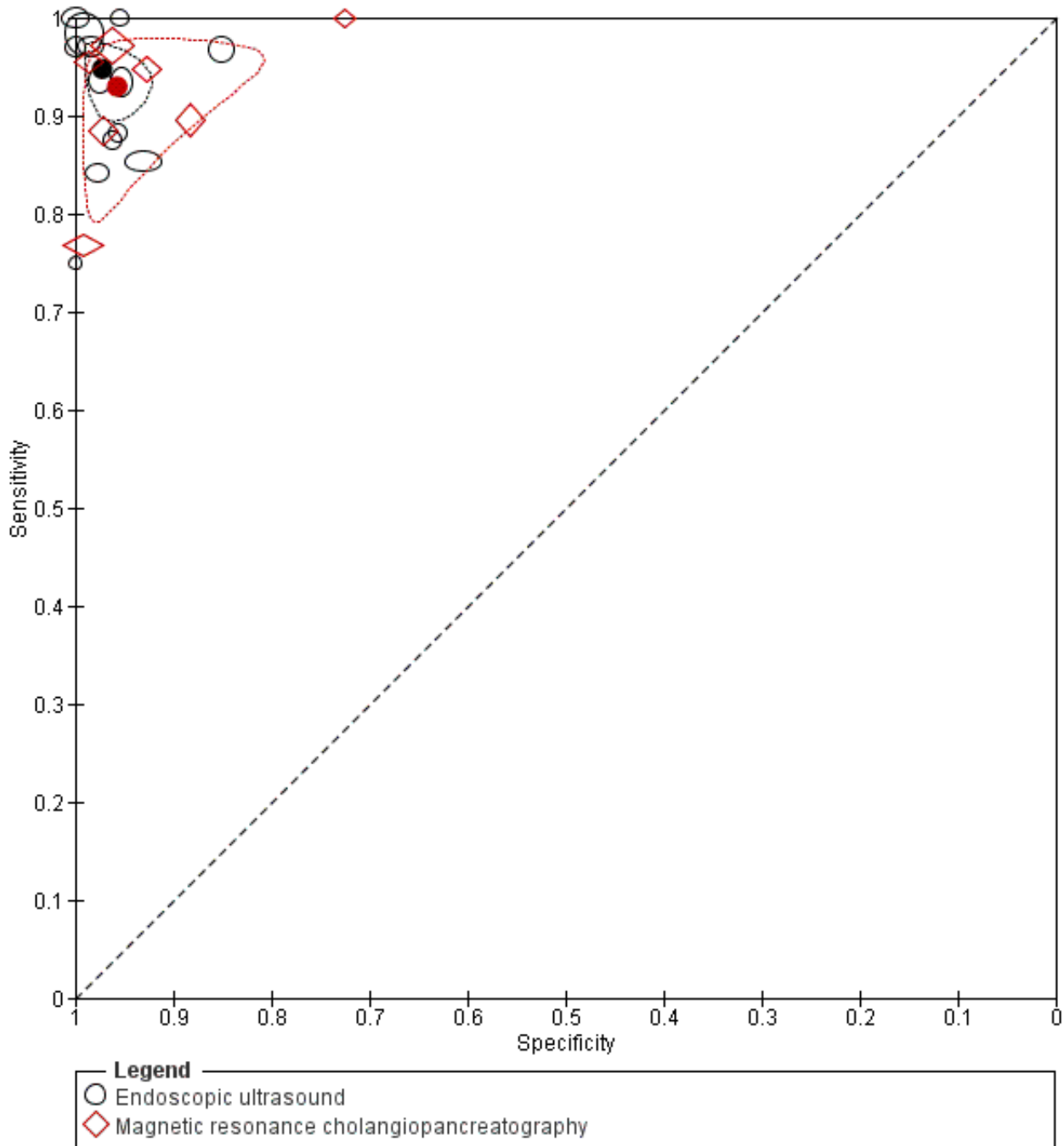


Figure 6. Summary ROC plot of endoscopic ultrasound and magnetic resonance cholangiopancreatography for diagnosis of common bile duct stones. For each test, each symbol represents the pair of sensitivity and specificity from a study and the symbol is scaled according to the sample size of the study. The solid circles represent the summary sensitivity and specificity for each test. Each summary point is surrounded by a 95% confidence region.



Endoscopic ultrasound (EUS)

The sensitivities of the 13 studies ranged between 0.75 and 1.00, and the specificities ranged between 0.85 and 1.00 (Figure 5). The summary sensitivity (95% CI) and summary specificity (95% CI) were 0.95 (95% CI 0.91 to 0.97) and 0.97 (95% CI 0.94 to 0.99). The summary positive and negative likelihood ratios were 34.4 (95%

CI 15.2 to 78.1) and 0.05 (95% CI 0.03 to 0.09). At the median pre-test probability of common bile duct stones of 41%, the post-test probabilities (with 95% CI) associated with positive and negative tests were 0.96 (95% CI 0.92 to 0.98) and 0.03 (95% CI 0.02 to 0.06) respectively. At the minimum pre-test probability of 14%, the post-test probabilities associated with positive and negative tests were

0.85 (95% CI 0.72 to 0.93) and 0.01 (95% CI 0.01 to 0.02). At the maximum pre-test probability of 68%, the post-test probabilities associated with positive and negative tests were 0.99 (95% CI 0.97 to 0.99) and 0.10 (95% CI 0.06 to 0.16).

Magnetic resonance cholangiopancreatography (MRCP)

The sensitivities ranged between 0.77 and 1.00, and the specificities ranged between 0.73 and 0.99 (Figure 5). The summary sensitivity (95% CI) and summary specificity (95% CI) were 0.93 (95% CI 0.87 to 0.96) and 0.96 (95% CI 0.89 to 0.98). The summary positive and negative likelihood ratios were 21.7 (95% CI 9.3 to 50.7) and 0.07 (95% CI 0.04 to 0.14). At the median pre-test probability of common bile duct stones of 41%, the post-test probabilities associated with positive and negative tests were 0.94 (95% CI 0.87 to 0.97) and 0.05 (95% CI 0.03 to 0.09). At the minimum pre-test probability of 14%, the post-test probabilities associated with positive and negative tests were 0.79 (95% CI 0.61 to 0.90) and 0.01 (95% CI 0.01 to 0.02). At the maximum pre-test probability of 68%, the post-test probabilities associated with positive and negative tests were 0.98 (95% CI 0.95 to 0.99) and 0.13 (95% CI 0.08 to 0.23).

Endoscopic ultrasound (EUS) versus magnetic resonance cholangiopancreatography (MRCP)

Only two studies (De Ledinghen 1999; Fernandez-Esparrach 2007) performed EUS and MRCP in the same participants and so we were unable to perform a direct comparison. We performed an indirect comparison of EUS and MRCP (Figure 6). There was no evidence of a difference in sensitivity or specificity between EUS and MRCP (P value = 0.5).

Investigation of sources of heterogeneity

We were unable to formally explore potential sources of heterogeneity for MRCP because there were only seven studies. For EUS, we found no evidence of a difference in sensitivity or specificity between full text publications (10 studies) and abstracts (3 studies) (P value = 0.5). The prevalence of common bile duct stones in the studies of EUS ranged between 16% and 63%. There was no evidence of an effect of prevalence on test performance (P value = 0.5).

We were unable to explore the effect of the following potential sources of heterogeneity.

1. Studies at low risk of bias versus those at unclear or high risk of bias: the analysis could not be performed because all the studies were of low methodological quality.
2. Prospective studies versus retrospective studies: eight studies were prospective, one was retrospective and four studies did not provide this information.
3. Symptomatic versus asymptomatic participants: this information was available in five studies only (Norton 1997; Montariol 1998; Buscarini 2003; Ney 2005; Choo 2012). All participants in these studies were symptomatic.
4. Proportion of patients with common bile duct strictures: the information was not available in any of the studies.
5. Proportion of patients with previous cholecystectomy: four studies did not include patients with previous cholecystectomy and five studies included between 8% and 100% of such patients.

Sensitivity analyses

Endoscopic ultrasound (EUS)

Two studies (Prat 1996; Buscarini 2003) reported participants with uninterpretable results together with their reference standard results. Five studies (Prat 1996; Montariol 1998; De Ledinghen 1999; Buscarini 2003; Fernandez-Esparrach 2007) reported uninterpretable results but did not provide the corresponding reference standard results. We did not perform sensitivity analyses because data were sparse.

Magnetic resonance cholangiopancreatography (MRCP)

None of the studies reported participants with uninterpretable results for whom the reference standard results were available and so we did not perform sensitivity analyses. Six studies (De Ledinghen 1999; Boraschi 2002; Gautier 2004; Guarise 2005; Miletic 2006; Fernandez-Esparrach 2007) reported participants with uninterpretable results for whom the reference standard results were not available.

DISCUSSION

Summary of main results

The results are summarised in Summary of findings 1. We included 13 studies that evaluated the diagnostic accuracy of EUS and seven studies that evaluated the diagnostic accuracy of MRCP. The summary sensitivity and specificity of EUS were 0.95 (95% CI 0.91 to 0.97) and 0.97 (95% CI 0.94 to 0.99). The summary sensitivity and specificity of MRCP were 0.93 (95% CI 0.87 to 0.96) and 0.96 (95% CI 0.89 to 0.98). Sensitivity and specificity did not differ significantly between the two tests. The median pre-test probability of common bile duct stones from the included studies was 41%. This proportion is higher than in the general population (Barbara 1987; Loria 1994) or in the population of patients undergoing cholecystectomy for gallbladder stones (Arnold 1979; Lill 2010; Yousefpour Azary 2011). This is probably due to the fact that EUS and MRCP are performed as triage tests in the second step of the diagnostic pathway, and only preselected patients with abnormal liver function tests or abnormal abdominal ultrasound, or both, were included in these studies. The probability of common bile duct stones in such a selected population has been reported to be about 36% (Rahman 2010), which is similar to the pre-test probability in this review. For a pre-test probability of 41%, the median observed in this review, the post-test probabilities associated with positive and negative EUS were 0.96 (95% CI 0.92 to 0.98) and 0.03 (95% CI 0.02 to 0.06). At the same pre-test probability, the post-test probabilities associated with positive and negative MRCP were 0.94 (95% CI 0.87 to 0.97) and 0.05 (95% CI 0.03 to 0.09).

The choice of whether to use MRCP or EUS will be based on the availability and expertise to perform these tests, and whether patients can tolerate the procedure. For example, MRCP may not be suitable for people with cardiac pacemakers or claustrophobia. Endoscopic ultrasound may not be suitable for people who have undergone gastric bypass procedures, including Roux-en-Y anastomosis for various indications such as cancer and obesity surgery. The proportion of people with such contra-indications to the tests is likely to be low and it is very unlikely that both tests will be unsuitable in the same person.

Strengths and weaknesses of the review

We conducted a thorough literature search and included full text publications and abstracts without any language restrictions. The use of diagnostic test accuracy filters may lead to the loss of some studies (Doust 2005) and so we did not use any diagnostic test accuracy filters. Two authors independently identified and extracted data from the studies, potentially decreasing errors related to single data extraction (Buscemi 2006). To avoid potential bias due to the use of an inadequate reference standard, we restricted the studies to those with appropriate reference standards.

The major limitation in the review process was our inability to formally explore all the potential sources of heterogeneity, as planned, because of limited data. Factors such as the proportion of participants with previous cholecystectomy may affect test accuracy but this information was not fully available. It was also not possible to perform a direct comparison of the tests because only two studies performed both tests in the same patients. Therefore, the evidence relies on an indirect test comparison which is prone to confounding and may give different results compared to a more reliable direct comparison (Takwoingi 2013). Endoscopic or surgical extraction was used in all participants in only seven studies (Prat 1996; De Ledinghen 1999; Boraschi 2002; Fazel 2002; Kohut 2002; Guarise 2005; Choo 2012). In the remaining 11 studies endoscopic or surgical clearance of the common bile duct was achieved in patients with a positive index test and clinical follow-up was performed in patients with a negative index test (Norton 1997; Canto 1998; Montariol 1998; Liu 2001; Jendresen 2002; Buscarini 2003; Gautier 2004; Ney 2005; Miletic 2006; Fernandez-Esparrach 2007; Ang 2012). This may result in overestimation of diagnostic accuracy although there was no evidence that this was the case. However, we acknowledge that even the best reference standard of endoscopic or surgical extraction of common bile duct stones can result in misclassification and hence an alteration in diagnostic accuracy if one or more stones reach the small bowel without the knowledge of the person who performed the common bile duct stone extraction. The use of different reference standards may also reflect the belief of the study authors about the probability of participants harbouring common bile duct stones. It is quite possible that in studies in which surgical or endoscopic clearance was performed in all participants (Prat 1996; De Ledinghen 1999; Boraschi 2002; Fazel 2002; Kohut 2002; Guarise 2005; Choo 2012) included participants were at greater risk of having common bile duct stones because of their symptoms (that is, they were more symptomatic) compared to those in which participants with a positive index test underwent surgical or endoscopic extraction of stones and participants with a negative index test were followed up clinically (Norton 1997; Canto 1998; Montariol 1998; Liu 2001; Jendresen 2002; Buscarini 2003; Gautier 2004; Ney 2005; Miletic 2006; Fernandez-Esparrach 2007; Ang 2012). This was not evident from pre-test probabilities of common bile duct stones in studies in which all participants underwent endoscopic or surgical extraction compared to those in which participants received different reference standards.

The major limitation of the included studies was that none of the studies were of good methodological quality. There was a high proportion of studies at high risk of bias and with high concern regarding applicability in all the four domains of the QUADAS-2 tool. This makes the validity of the results questionable. We considered

endoscopic or surgical extraction of common bile duct stones in all participants as a better reference standard than a combination of extraction of common bile duct stones in participants with a positive index test and clinical follow-up in those with a negative index test. However, we acknowledge that even this ideal reference standard can result in misclassification and hence an alteration in diagnostic test accuracy if one or more stones reach the small bowel without the knowledge of the person performing the extraction. Despite these shortcomings, these studies provide the best available evidence on the topic.

There are other published systematic reviews on diagnostic accuracy of EUS and MRCP for common bile duct stones (Mark 2002; Verma 2006; Ledro-Cano 2007; McMahon 2008). The summary sensitivity of EUS in these systematic reviews ranged from 90% to 93%, and specificity ranged from 96% to 99%. The summary sensitivity of MRCP ranged from 85% to 87% and specificity ranged from 93% to 95%. In general, in spite of differences in the methods used, the summary sensitivities and specificities appear broadly similar between these reviews and the current review.

Applicability of findings to the review question

Most of the participants included in the review had prior abnormal transabdominal ultrasound or liver function tests or were symptomatic, and so the findings of this review are only applicable to such people. The diagnostic accuracy in asymptomatic people with normal ultrasound and liver function tests may be different. The methods of EUS and MRCP that were used in the included studies have not changed considerably over time and so the results from old studies (the earliest publication included in this review was in 1996 for EUS and 1999 for MRCP) are still applicable. The reference standard that we used in this review is a reliable reference standard and so the findings are applicable to the review question. However, it should be noted that the tests were performed in secondary or tertiary centres and our findings are therefore applicable only in this setting. The decision to use these tests as triage tests prior to confirmation with invasive tests in a state-funded health system is dependent upon a formal cost-utility analysis, which is beyond the scope of this review.

In this review, we have assessed the diagnostic test accuracy of EUS and MRCP in the diagnosis of common bile duct stones. The diagnostic accuracy of these tests for the diagnosis of other conditions such as benign or malignant biliary stricture and periampullary tumours have not been assessed in this review.

AUTHORS' CONCLUSIONS

Implications for practice

Both EUS and MRCP have high diagnostic accuracy for detection of common bile duct stones. People with positive EUS or MRCP should undergo endoscopic or surgical extraction of common bile duct stones, and those with negative EUS or MRCP do not need further invasive tests. However, further investigations will be indicated if symptoms persist. The two tests are similar in terms of diagnostic accuracy; the choice of which test to use will be informed by availability and contra-indications to each test. However, it should be noted that the results are based on studies that are of poor methodological quality and so the results should be interpreted with caution.

Implications for research

Further studies of high methodological quality are necessary. Future research should be conducted in a prospective manner as close as possible to the clinical setting in which EUS and MRCP would be used. Such research should use appropriate reference standards and should not use ERCP or IOC as the reference standards because neither of these tests are 100% accurate (Gurusamy 2015a). We acknowledge that differential verification cannot always be avoided if endoscopic sphincterotomy and extraction of stones are used as the reference standard because of the complications associated with this procedure (Gurusamy 2011). Surgical exploration of the common bile duct is a major surgical procedure and cannot be undertaken lightly. Based on these considerations, persons with a positive test are likely to undergo endoscopic sphincterotomy and extraction of stones or surgical exploration of the common bile duct while those with a negative test are likely to be followed up. Such persons should be followed up for at least six months to ensure that they do not develop the symptoms of common bile duct stones. Future studies should avoid any inappropriate exclusions to ensure that true diagnostic accuracy can be determined. Long-term follow-up of patients with negative tests will help in understanding the implications of false negative results and will aid clinical decision making.

Both EUS and MRCP involve additional costs. Whether these additional costs are offset by avoiding unnecessary invasive testing in a state-funded healthcare system has to be investigated in formal cost-effectiveness analysis.

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CHARACTERISTICS OF STUDIES
Characteristics of included studies [ordered by study ID]

Ang 2012
Study characteristics

Patient sampling	Type of study: retrospective study Consecutive or random sample: consecutive patients
Patient characteristics and setting	Sample size: 112 Females: not stated Age: 61 years Presentation: Inclusion criteria Patients with a high clinical probability of CBD stone defined as following 1. Recent episode of acute cholangitis 2. Acute gallstone pancreatitis with cholestatic liver function test 3. Cholestatic jaundice 4. Alkaline phosphatase elevation > 2-fold 5. Dilated CBD Setting: secondary care (Department of Gastroenterology, Singapore)
Index tests	Index test: endoscopic ultrasound Technical specifications: not stated Performed by: not stated

Ang 2012 (Continued)

Criteria for positive diagnosis: not stated

Target condition and reference standard(s)

 Target condition: common bile duct stones
 Reference standard: endoscopic extraction of stones in patients with positive EUS and clinical follow-up minimum 6 months in patients with negative EUS
 Technical specifications: not applicable
 Performed by: endoscopists and clinicians
 Criteria for positive diagnosis: endoscopic extraction of stones in patients with positive EUS and clinical follow-up minimum 6 months in patients with negative EUS

Flow and timing

 Number of indeterminates for whom the results of reference standard was available: not stated
 Number of patients who were excluded from the analysis: not stated

Comparative

Notes

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
		Low	Low
DOMAIN 2: Index Test EUS			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
		High	High
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
		High	High
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	No		

Ang 2012 (Continued)

Were all patients included in the analysis? Unclear

High
Boraschi 2002
Study characteristics

Patient sampling	Type of study: unclear whether prospective or retrospective study Consecutive or random sample: unclear
Patient characteristics and setting	Sample size: 97 Females: 56 (58.9%) Age: 63 years Presentation: Inclusion criteria 1. Elevation of biochemical parameters of cholestasis (alkaline phosphatase, gamma glutamyl transpeptidase, aspartate aminotransferase, alanine aminotransferase, and bilirubin) 2. Clinical or enzymatic pancreatitis 3. Common bile duct size at least 6.5 mm at ultrasound Setting: secondary care (Italy)
Index tests	Index test: magnetic resonance cholangiopancreatography Technical specifications: 0.5 T magnet; GE Performed by: two experienced radiologists jointly Criteria for positive diagnosis: foci of intraluminal signal void on T2-weighted sequences
Target condition and reference standard(s)	Target condition: common bile duct stones Reference standard: attempted endoscopic, laparoscopic or surgical extraction of CBD stones Technical specifications: not applicable Performed by: endoscopists and surgeons Criteria for positive diagnosis: presence or absence of stones during endoscopic or surgical clearance
Flow and timing	Number of indeterminates for whom the results of reference standard was available: not stated Number of patients who were excluded from the analysis: 2 (2.1%)

Comparative

Notes

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		

Boraschi 2002 *(Continued)*

		High	High
DOMAIN 2: Index Test MRCP			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
		Low	Low
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
		High	Low
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	No		
		High	

Buscarini 2003

Study characteristics	
Patient sampling	Type of study: prospective study Consecutive or random sample: consecutive patients
Patient characteristics and setting	Sample size: 459 Females: 283 (61.7%) Age: 66 years Presentation: Inclusion criteria Patients with suspected choledocholithiasis based on one of the following criteria: <ol style="list-style-type: none"> 1. History of biliary-type colicky pain or recent cholangitis, and a history of jaundice 2. Recent acute pancreatitis 3. Serum bilirubin and/or alkaline phosphatase or 7-glutamyl transpeptidase or aminotransferases more than twice the upper normal limit, or both 4. Dilatation of the intrahepatic or extrahepatic bile ducts (> 7 mm) or a suspicion of choledocholithiasis on transabdominal US or CT, or both Exclusion criteria: <ol style="list-style-type: none"> 1. Any factor that rendered the patient unsuitable for treatment of choledocholithiasis 2. Previous gastrectomy 3. Patients with a definite transabdominal ultrasound diagnosis of choledocholithiasis

Buscarini 2003 (Continued)

Setting: secondary care (Gastroenterology Department in Italy)

Index tests	Index test: endoscopic ultrasound Technical specifications: GF-UM20; Olympus; 7.5 to 12 MHz probe Performed by: endoscopist with at least 3 years' experience Criteria for positive diagnosis: echo-rich structures, possibly moving within the bile duct, with or without acoustic shadowing
Target condition and reference standard(s)	Target condition: common bile duct stones Reference standard: endoscopic or surgical extraction of stones in patients with positive EUS and clinical follow-up minimum 7 months in patients with negative EUS Technical specifications: not applicable Performed by: endoscopists, surgeons, and clinicians Criteria for positive diagnosis: endoscopic or surgical extraction of stones in patients with positive EUS and clinical follow-up minimum 7 months in patients with negative EUS
Flow and timing	Number of indeterminates for whom the results of reference standard were available: 4 (0.8%) Number of patients who were excluded from the analysis: 22 (4.3%)
Comparative	
Notes	

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
		Low	Low
DOMAIN 2: Index Test EUS			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
		Low	Low
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
		High	High

Buscarini 2003 (Continued)

DOMAIN 4: Flow and Timing

Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive the same reference standard?	No
Were all patients included in the analysis?	No
High	

Canto 1998
Study characteristics

Patient sampling	Type of study: prospective study Consecutive or random sample: consecutive patients
Patient characteristics and setting	Sample size: 64 Females: 42 (65.6%) Age: 53 years Presentation: Inclusion criteria Patients with suspected choledocholithiasis based on two or more of the following: <ol style="list-style-type: none"> 1. Right upper quadrant or epigastric pain 2. Abnormal serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), serum alkaline phosphatase, or total bilirubin 3. History of acute pancreatitis 4. Recent or current acute cholangitis 5. Biliary dilatation on transabdominal US or CT 6. Choledocholithiasis diagnosed by US, CT, or endoscopic retrograde cholangiopancreatography previously performed at another institution Exclusion criteria <ol style="list-style-type: none"> 1. Haemodynamically unstable patients Setting: secondary care (Gastroenterology Department, USA)
Index tests	Index test: endoscopic ultrasound Technical specifications: EU-M20; Olympus; 7.5 MHz probe Performed by: experienced endosonographer Criteria for positive diagnosis: a reproducible hyperechoic focus within the extrahepatic bile duct with associated acoustic shadowing
Target condition and reference standard(s)	Target condition: common bile duct stones Reference standard: endoscopic or surgical extraction of stones in patients with positive EUS and clinical follow-up minimum 12 months in patients with negative EUS Technical specifications: not applicable Performed by: endoscopists, surgeons, and clinicians Criteria for positive diagnosis: endoscopic or surgical extraction of stones in patients with positive EUS and clinical follow-up minimum 12 months in patients with negative EUS
Flow and timing	Number of indeterminates for whom the results of reference standard was available: not stated Number of patients who were excluded from the analysis: not stated

Canto 1998 (Continued)

Comparative

Notes

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
		Low	Low
DOMAIN 2: Index Test EUS			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
		Low	Low
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
		High	High
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	No		
Were all patients included in the analysis?	Unclear		
		High	

Choo 2012
Study characteristics

Patient sampling	Type of study: prospective study Consecutive or random sample: consecutive patients
Patient characteristics and setting	Sample size: 9. Females: 8 (88.8%) Age: 37 years Presentation: Inclusion criteria Patients who had positive intraoperative cholangiogram Setting: secondary care (Department of Gastroenterology, USA)
Index tests	Index test: endoscopic ultrasound Technical specifications: not stated Performed by: physician Criteria for positive diagnosis: not stated
Target condition and reference standard(s)	Target condition: common bile duct stones Reference standard: attempted endoscopic extraction of stones in all patients Technical specifications: not applicable Performed by: endoscopist Criteria for positive diagnosis: presence or absence of stones during endoscopic clearance
Flow and timing	Number of indeterminates for whom the results of reference standard was available: not stated Number of patients who were excluded from the analysis: not stated
Comparative	
Notes	

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
		Low	High
DOMAIN 2: Index Test EUS			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
		Low	High
DOMAIN 3: Reference Standard			

Choo 2012 (Continued)

Is the reference standards likely to correctly classify the target condition? Yes

Were the reference standard results interpreted without knowledge of the results of the index tests? Yes

Low
Low
DOMAIN 4: Flow and Timing

Was there an appropriate interval between index test and reference standard? Yes

Did all patients receive the same reference standard? Yes

Were all patients included in the analysis? Unclear

High
De Ledinghen 1999
Study characteristics

Patient sampling Type of study: prospective study
 Consecutive or random sample: unclear

Patient characteristics and setting Sample size: 43
 Females: 25 (58.1%)
 Age: 61 years
 Presentation:
 Inclusion criteria
 Patients with clinical or biochemical signs of choledocholithiasis according to the following criteria:
 1. Combination of epigastric or right upper quadrant pain with fever or jaundice
 2. One or two of the previous signs together with an elevation of serum alkaline phosphatase level or an elevation of serum gamma glutamyl transpeptidase or transaminase level more than the upper limit of normal
 3. Acute pancreatitis
 4. Unexplained cholestasis defined by an elevation of serum alkaline phosphatase level and an elevation of serum gamma glutamyl transpeptidase level to more than two times the upper limit of normal
 Exclusion criteria
 1. Long-term daily alcohol intake exceeded 80 g
 2. Taking a hepatotoxic drug
 3. Serum hepatitis B or C antibodies were present
 Setting: secondary care (Hepatogastroenterology Department, France)

Index tests Index test: magnetic resonance cholangiopancreatography
 Technical specifications: 1 T magnet; Siemens
 Performed by: two experienced radiologists jointly
 Criteria for positive diagnosis: a round, oval, or multifaceted area of signal void (hypointensity) was present within the lumen of the hyperintense bile duct

 Index test: endoscopic ultrasound
 Technical specifications: GF EUM20; Olympus
 Performed by: not stated

De Ledinghen 1999 (Continued)

Criteria for positive diagnosis: a hyperechoic structure within the common bile duct sometimes associated with an acoustic shadow

Target condition and reference standard(s)

Target condition: common bile duct stones
 Reference standard: attempted endoscopic or surgical extraction of stones in all patients
 Technical specifications: not applicable
 Performed by: endoscopists and surgeons
 Criteria for positive diagnosis: presence or absence of stones during endoscopic or surgical clearance

Flow and timing

Number of indeterminates for whom the results of reference standard was available: not stated
 Number of patients who were excluded from the analysis: 11 (25.6%)

Comparative

Notes

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
		High	High
DOMAIN 2: Index Test MRCP			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
		Low	Low
DOMAIN 2: Index Test EUS			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
		Low	Low
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		

De Ledinghen 1999 (Continued)

	High	Low
DOMAIN 4: Flow and Timing		
Was there an appropriate interval between index test and reference standard?	Unclear	
Did all patients receive the same reference standard?	Yes	
Were all patients included in the analysis?	No	
High		

Fazel 2002

Study characteristics	
Patient sampling	Type of study: unclear whether prospective or retrospective study Consecutive or random sample: unclear
Patient characteristics and setting	Sample size: 40 Females: not stated Age: not stated Presentation: Inclusion criteria Patients with suspicion of biliary stone disease on the basis of symptoms and signs suggestive of choledocholithiasis (biliary colic, abnormal liver function tests, or abnormal transabdominal ultrasound) Setting: care setting not stated, USA
Index tests	Index test: endoscopic ultrasound Technical specifications: not stated Performed by: not stated Criteria for positive diagnosis: not stated
Target condition and reference standard(s)	Target condition: common bile duct stones Reference standard: attempted endoscopic extraction of stones in all patients Technical specifications: not applicable Performed by: endoscopists and surgeons Criteria for positive diagnosis: presence or absence of stones during endoscopic or surgical clearance
Flow and timing	Number of indeterminates for whom the results of reference standard was available: not stated Number of patients who were excluded from the analysis: not stated
Comparative	
Notes	
Methodological quality	

Fazel 2002 (Continued)

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
		High	High
DOMAIN 2: Index Test EUS			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
		High	High
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
		High	Low
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Unclear		
		High	

Fernandez-Esparrach 2007
Study characteristics

Patient sampling	Type of study: prospective study Consecutive or random sample: consecutive patients
Patient characteristics and setting	Sample size: 159 Females: 74 (46.5%) Age: 68 years Presentation: Inclusion criteria 1. Unexplained common bile duct dilation in standard US, independently of clinical symptoms

Fernandez-Esparrach 2007 (Continued)

2. Non-dilated common bile duct and a high probability of having choledocholithiasis (cholangitis, jaundice, non-severe pancreatitis, alkaline phosphatase < twice the upper normal limit or increased gamma glutamyl transferase, alanine aminotransferase or aspartate aminotransferase)
 Exclusion criteria

1. Acute severe biliary pancreatitis

Setting: secondary care (Gastroenterology and Surgery Departments, Spain)

Index tests	<p>Index test: magnetic resonance cholangiopancreatography Technical specifications: 1.5 T magnet; Siemens Performed by: not stated Criteria for positive diagnosis: a round, oval, or multifaceted area of signal void (hypointensity) was present inside the lumen of the hyperintense bile duct</p> <p>Index test: endoscopic ultrasound Technical specifications: GF UM20 or GF UM160; Olympus Performed by: not stated Criteria for positive diagnosis: visualisation of one or more hyperechoic images inside the common bile duct with or without acoustic shadow</p>
Target condition and reference standard(s)	<p>Target condition: common bile duct stones Reference standard: endoscopic or surgical extraction of stones in patients with positive EUS and clinical follow-up of minimum 6 months in patients with negative EUS Technical specifications: not applicable Performed by: endoscopists, surgeons, and clinicians Criteria for positive diagnosis: endoscopic or surgical extraction of stones in patients with positive EUS and clinical follow-up of minimum 6 months in patients with negative EUS</p>
Flow and timing	<p>Number of indeterminates for whom the results of reference standard was available: not stated Number of patients who were excluded from the analysis: 24 (15.1%)</p>
Comparative	
Notes	

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
		Low	Low
DOMAIN 2: Index Test MRCP			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
		High	Low
DOMAIN 2: Index Test EUS			

Fernandez-Esparrach 2007 *(Continued)*

Were the index test results interpreted without knowledge of the results of the reference standard? Unclear

High
Low
DOMAIN 3: Reference Standard

Is the reference standards likely to correctly classify the target condition? Yes

Were the reference standard results interpreted without knowledge of the results of the index tests? Unclear

High
High
DOMAIN 4: Flow and Timing

Was there an appropriate interval between index test and reference standard? Unclear

Did all patients receive the same reference standard? No

Were all patients included in the analysis? No

High
Gautier 2004
Study characteristics

Patient sampling Type of study: prospective study
 Consecutive or random sample: consecutive patients

Patient characteristics and setting Sample size: 108
 Females: 58 (53.7%)
 Age: 59 years
 Presentation:
 Inclusion criteria
 Patients with suspected common bile duct stones
 Exclusion criteria
 1. Patients with a contraindication for magnetic resonance imaging (pacemaker, intraocular metallic implant)
 2. Initial differential or positive diagnosis of CBDS had been established on the basis of ultrasound or computed tomography
 Setting: secondary care (Radiology Department, France)

Index tests Index test: magnetic resonance cholangiopancreatography
 Technical specifications: 1.5 T magnet; Siemens

Gautier 2004 (Continued)

Performed by: two radiologists interpreted the scan independently and in the case of discrepancy, a third radiologist made the final decision
 Criteria for positive diagnosis: low intensity intraductal signal surrounded by a high intensity liquid signal

Target condition and reference standard(s)

Target condition: common bile duct stones
 Reference standard: endoscopic or surgical extraction of stones or clinical follow-up of minimum 6 months
 Technical specifications: not applicable
 Performed by: endoscopists, surgeons, and clinicians
 Criteria for positive diagnosis: endoscopic, surgical extraction of stones, clinical follow-up of minimum 6 months

Flow and timing

Number of indeterminates for whom the results of reference standard was available: not stated
 Number of patients who were excluded from the analysis: 9 (8.3%)

Comparative

Notes

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
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DOMAIN 1: Patient Selection

Was a consecutive or random sample of patients enrolled?	Yes		
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Was a case-control design avoided?	Yes		
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Low

Low

DOMAIN 2: Index Test MRCP

Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
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High

Low

DOMAIN 3: Reference Standard

Is the reference standards likely to correctly classify the target condition?	Yes		
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Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
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High

High

DOMAIN 4: Flow and Timing

Gautier 2004 (Continued)

Was there an appropriate interval between index test and reference standard? Yes

Did all patients receive the same reference standard? No

Were all patients included in the analysis? No

High

Guarise 2005
Study characteristics

Patient sampling	Type of study: unclear whether prospective or retrospective study Consecutive or random sample: consecutive patients
Patient characteristics and setting	Sample size: 170 Females: not stated Age: not stated Presentation: Inclusion criteria Patients who underwent magnetic resonance cholangiopancreatography and endoscopic retrograde cholangiopancreatography for clinically suspected biliary disease Setting: secondary care (Radiology Department, Italy)
Index tests	Index test: magnetic resonance cholangiopancreatography Technical specifications: 1.5 T magnet; Siemens Performed by: two radiologists with experience in gastrointestinal disease Criteria for positive diagnosis: a rounded and oval signal defect within the bile duct in at least two projections and located in the dependent portion of the duct
Target condition and reference standard(s)	Target condition: common bile duct stones Reference standard: endoscopic extraction of stones in all patients Technical specifications: not applicable Performed by: endoscopists (the images were interpreted as consensus with radiologist) Criteria for positive diagnosis: endoscopic extraction of stones in all patients
Flow and timing	Number of indeterminates for whom the results of reference standard was available: not stated Number of patients who were excluded from the analysis: 23 (13.5%)

Comparative

Notes

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
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DOMAIN 1: Patient Selection

Guarise 2005 (Continued)

Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
		Low	Low
DOMAIN 2: Index Test MRCP			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
		High	Low
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
		Low	Low
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	No		
		High	

Jendresen 2002
Study characteristics

Patient sampling	Type of study: prospective study Consecutive or random sample: consecutive patients
Patient characteristics and setting	Sample size: 180 Females: 129 (71.7%) Age: not stated Presentation: Inclusion criteria Patients with symptomatic cholelithiasis Setting: secondary care (Surgery, Surgical Gastroenterology, and Radiology Departments, Denmark)
Index tests	Index test: magnetic resonance cholangiopancreatography

Jendresen 2002 (Continued)

Technical specifications: Gyroscan T5-NT Powertrack 1000; Phillips
 Performed by: one radiologist
 Criteria for positive diagnosis: areas of low signal in the surrounding signal-intense bile

Target condition and reference standard(s)	Target condition: common bile duct stones Reference standard: endoscopic extraction of stones or clinical follow-up of minimum 6 months Technical specifications: not applicable Performed by: endoscopists and clinicians Criteria for positive diagnosis: endoscopic extraction of stones or clinical follow-up of minimum 6 months
Flow and timing	Number of indeterminates for whom the results of reference standard was available: not stated Number of patients who were excluded from the analysis: not stated
Comparative	
Notes	

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
		Low	Low
DOMAIN 2: Index Test MRCP			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
		Low	Low
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	No		
		High	High
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		

Jendresen 2002 (Continued)

Did all patients receive the same reference standard? No

Were all patients included in the analysis? Yes

High

Kohut 2002
Study characteristics

Patient sampling Type of study: prospective study
 Consecutive or random sample: unclear

Patient characteristics and setting Sample size: 134
 Females: 109 (81.3%)
 Age: 57 years
 Presentation:
 Inclusion criteria
 Patients suspected of having common bile duct stones based on the following features
 1. Biliary colic with elevated levels of biochemical values (bilirubin, transaminases, alkaline phosphatase, g-glutamyl transpeptidase), and enlarged bile ducts (> 7 mm in patients with gallbladder in situ or > 9 mm in post-cholecystectomy patients) or suspicion of bile duct stones on conventional ultrasound, done currently or in the previous 6 months
 Exclusion criteria
 1. Patients with suspicion of biliary or pancreatic malignancy on CT scan
 2. Current acute biliary pancreatitis or cholangitis, or both
 Setting: secondary care (Gastroenterology Departments, Poland)

Index tests Index test: endoscopic ultrasound
 Technical specifications: FG 32 UA; Pentax
 Performed by: not stated
 Criteria for positive diagnosis: single or multiple hyperechoic structures within the biliary tree with acoustic shadowing were found

Target condition and reference standard(s) Target condition: common bile duct stones
 Reference standard: attempted endoscopic or surgical extraction of stones in all patients
 Technical specifications: not applicable
 Performed by: endoscopists and surgeons
 Criteria for positive diagnosis: presence or absence of stones during endoscopic or surgical clearance

Flow and timing Number of indeterminates for whom the results of reference standard was available: not stated
 Number of patients who were excluded from the analysis: not stated

Comparative

Notes

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
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Kohut 2002 *(Continued)*
DOMAIN 1: Patient Selection

Was a consecutive or random sample of patients enrolled? Unclear

Was a case-control design avoided? Yes

High

High

DOMAIN 2: Index Test EUS

Were the index test results interpreted without knowledge of the results of the reference standard? Unclear

High

Low

DOMAIN 3: Reference Standard

Is the reference standards likely to correctly classify the target condition? Yes

Were the reference standard results interpreted without knowledge of the results of the index tests? Unclear

High

Low

DOMAIN 4: Flow and Timing

Was there an appropriate interval between index test and reference standard? Yes

Did all patients receive the same reference standard? Yes

Were all patients included in the analysis? Unclear

High

Liu 2001
Study characteristics

Patient sampling Type of study: prospective study
 Consecutive or random sample: consecutive patients

Patient characteristics and setting Sample size: 100
 Females: 49 (49.0%)
 Age: 61 years
 Presentation:
 Inclusion criteria

Liu 2001 (Continued)

1. Patients presenting with acute pancreatitis

Exclusion criteria

1. Known diagnosis of recurrent pancreatitis related to chronic alcoholism or hyperlipidaemia
2. Post-endoscopic retrograde cholangiopancreatography pancreatitis when performed for reasons other than suspected biliary stones

Setting: secondary care (Surgery Department, Hong Kong, China)

Index tests

Index test: endoscopic ultrasound

Technical specifications: GF-UM20 or JF-UM20; Olympus; 7.5 MHz probe

Performed by: endoscopist

Criteria for positive diagnosis: a persistent echogenic focus with or without posterior acoustic shadowing was considered a biliary stone, microlithiasis, or sludge

Target condition and reference standard(s)

Target condition: common bile duct stones

Reference standard: endoscopic extraction of stones in patients with positive EUS and clinical follow-up of minimum 12 months in patients with negative EUS

Technical specifications: not applicable

Performed by: endoscopists, surgeons, and clinicians

Criteria for positive diagnosis: endoscopic extraction of stones in patients with positive EUS and clinical follow-up of minimum 12 months in patients with negative EUS

Flow and timing

Number of indeterminates for whom the results of reference standard was available: not stated

Number of patients who were excluded from the analysis: not stated

Comparative

Notes

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
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DOMAIN 1: Patient Selection

Was a consecutive or random sample of patients enrolled?	Yes		
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Was a case-control design avoided?	Yes		
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Low

Low

DOMAIN 2: Index Test EUS

Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
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High

Low

DOMAIN 3: Reference Standard

Is the reference standards likely to correctly classify the target condition?	Yes		
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Liu 2001 (Continued)

Were the reference standard results interpreted without knowledge of the results of the index tests? Unclear

High
High
DOMAIN 4: Flow and Timing

Was there an appropriate interval between index test and reference standard? Yes

Did all patients receive the same reference standard? No

Were all patients included in the analysis? Yes

High
Miletic 2006
Study characteristics

Patient sampling Type of study: prospective study
 Consecutive or random sample: consecutive patients

Patient characteristics and setting Sample size: 337
 Females: 174 (51.6%)
 Age: 65 years
 Presentation:
 Inclusion criteria
 Patients with suspected CBD stones undergoing magnetic resonance cholangiopancreatography
 Setting: secondary care (Croatia)

Index tests Index test: magnetic resonance cholangiopancreatography
 Technical specifications: 0.5 T magnet; Shimadzu
 Performed by: two radiologists interpreted the scan independently and arrived at a consensus
 Criteria for positive diagnosis: not stated

Target condition and reference standard(s) Target condition: common bile duct stones
 Reference standard: endoscopic or surgical extraction of stones in patients and clinical follow-up of minimum 12 months in patients with negative endoscopic retrograde cholangiopancreatography
 Technical specifications: not applicable
 Performed by: endoscopists, surgeons, and clinicians
 Criteria for positive diagnosis: endoscopic or surgical extraction of stones in patients and clinical follow-up of minimum 12 months in patients with negative endoscopic retrograde cholangiopancreatography

Flow and timing Number of indeterminates for whom the results of reference standard was available: not stated
 Number of patients who were excluded from the analysis: 29 (8.6%)

Miletic 2006 *(Continued)*

Comparative

Notes

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
		Low	Low
DOMAIN 2: Index Test MRCP			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
		High	High
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
		High	High
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	No		
Were all patients included in the analysis?	No		
		High	

Montariol 1998
Study characteristics

Patient sampling	Type of study: prospective study Consecutive or random sample: consecutive patients
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Montariol 1998 (Continued)

Patient characteristics and setting	Sample size: 240 Females: 171 (71.3%) Age: 57 years Presentation: Inclusion criteria 1. Patients with symptomatic cholelithiasis, scheduled for elective cholecystectomy or emergency operations within 48 hours for acute cholecystitis Exclusion criteria 1. Cholelithiasis was asymptomatic 2. Preoperative risk of CBD stones was less than 5% 3. Patients had symptomatic choledocholithiasis defined as combination of clinical symptoms (pancreatic pain and jaundice), biochemical abnormalities (serum aminotransferase, alkaline phosphatase or γ -glutamyl transpeptidase levels more than twice normal values, serum bilirubin levels $>50 \mu\text{mol/L}$, and serum amylase and lipase levels more than fourfold and threefold, respectively), and morphologic features (presence of hyperechoic image in the CBD on ultrasonography Setting: secondary care (Surgery Departments, France)		
Index tests	Index test: endoscopic ultrasound Technical specifications: EUM3 and EUM20; Olympus; 7.5 MHz probe Performed by: experienced and selected operators Criteria for positive diagnosis: stones were described as hyperechoic images in the different parts of the CBD, identified because of their acoustic shadow and usually mobile spontaneously or with changing positions		
Target condition and reference standard(s)	Target condition: common bile duct stones Reference standard: surgical extraction of stones in patients with positive EUS and clinical follow-up of minimum 12 months in patients with negative EUS Technical specifications: not applicable Performed by: surgeons and clinicians Criteria for positive diagnosis: surgical extraction of stones in patients with positive EUS and clinical follow-up of minimum 12 months in patients with negative EUS		
Flow and timing	Number of indeterminates for whom the results of reference standard was available: not stated Number of patients who were excluded from the analysis: 25 (10.4%)		
Comparative			
Notes			
Methodological quality			
Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
		Low	Low
DOMAIN 2: Index Test EUS			
Were the index test results interpreted without knowledge	Unclear		

Montariol 1998 (Continued)
 of the results of the reference
 standard?

	High	Low
DOMAIN 3: Reference Standard		
Is the reference standards likely to correctly classify the target condition?	Yes	
Were the reference standard results interpreted without knowledge of the results of the index tests?	No	
	High	High
DOMAIN 4: Flow and Timing		
Was there an appropriate interval between index test and reference standard?	Yes	
Did all patients receive the same reference standard?	No	
Were all patients included in the analysis?	No	
	High	

Ney 2005

Study characteristics

Patient sampling	Type of study: prospective study Consecutive or random sample: consecutive patients
Patient characteristics and setting	Sample size: 68 Females: 49 (72.1%) Age: 57 years Presentation: Inclusion criteria 1. Dilated CBD (> 7 mm on conventional ultrasound) and/or hepatic biochemical parameter abnormalities (AST > 2 times normal; elevated alkaline phosphatase) Exclusion criteria 1. Jaundiced or had clinical signs of cholangitis 2. Acute pancreatitis 3. Unequivocal evidence of CBD stones on US or CT scans or magnetic resonance cholangiopancreatography Setting: secondary care (Surgery Department, Brazil)
Index tests	Index test: endoscopic ultrasound Technical specifications: GIF-UM20; Olympus; 7.5 or 12 MHz probe Performed by: not stated

Ney 2005 (Continued)

Criteria for positive diagnosis: stones were defined as mobile hyperechoic spots with an acoustic shadow

Target condition and reference standard(s)

Target condition: common bile duct stones
 Reference standard: endoscopic or surgical extraction of stones in patients with positive EUS and clinical follow-up minimum 11 months in patients with negative EUS
 Technical specifications: not applicable
 Performed by: endoscopists, surgeons, and clinicians
 Criteria for positive diagnosis: endoscopic or surgical extraction of stones in patients with positive EUS and clinical follow-up minimum 11 months in patients with negative EUS

Flow and timing

Number of indeterminates for whom the results of reference standard was available: not stated
 Number of patients who were excluded from the analysis: not stated

Comparative

Notes

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
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DOMAIN 1: Patient Selection

Was a consecutive or random sample of patients enrolled?	Yes		
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Was a case-control design avoided?	Yes		
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Low

Low

DOMAIN 2: Index Test EUS

Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
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High

Low

DOMAIN 3: Reference Standard

Is the reference standards likely to correctly classify the target condition?	Yes		
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Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
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High

High

DOMAIN 4: Flow and Timing

Was there an appropriate interval between index test and reference standard?	Yes		
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Ney 2005 (Continued)

Did all patients receive the same reference standard? No

Were all patients included in the analysis? Yes

High

Norton 1997
Study characteristics

Patient sampling	Type of study: unclear whether prospective or retrospective study Consecutive or random sample: unclear
Patient characteristics and setting	Sample size: 50 Females: 34 (68.0%) Age: 63 years Presentation: Inclusion criteria Patients with proven symptomatic gallstone disease and suspected bile duct stones because of the presence of at least one of the following features 1. Dilated (greater than 7 mm) bile duct on abdominal ultrasonography 2. Clinical jaundice 3. Gallstone pancreatitis 4. Deranged liver function Setting: secondary care (Surgery Department, United Kingdom)
Index tests	Index test: endoscopic ultrasound Technical specifications: GF-UM 20; Olympus Performed by: not stated Criteria for positive diagnosis: stones were recognized by their hyperechoic image and the acoustic shadow commonly produced
Target condition and reference standard(s)	Target condition: common bile duct stones Reference standard: endoscopic or surgical extraction of stones in patients with positive EUS and clinical follow-up minimum 6 months in patients with negative EUS Technical specifications: not applicable Performed by: endoscopists, surgeons, and clinicians Criteria for positive diagnosis: endoscopic or surgical extraction of stones in patients with positive EUS and clinical follow-up minimum 6 months in patients with negative EUS
Flow and timing	Number of indeterminates for whom the results of reference standard was available: not stated Number of patients who were excluded from the analysis: not stated

Comparative

Notes

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
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DOMAIN 1: Patient Selection

Norton 1997 (Continued)

Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
		High	High
DOMAIN 2: Index Test EUS			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
		High	Low
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
		High	High
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	No		
Were all patients included in the analysis?	Unclear		
		High	

Prat 1996
Study characteristics

Patient sampling	Type of study: prospective Consecutive or random sample: consecutive patients
Patient characteristics and setting	Sample size: 121 Females: 69 (57.0%) Age: 70 years Presentation: Inclusion criteria 1. Strong suspicion of choledocholithiasis as determined by a combination of clinical symptoms (history of biliary colic, pancreatic pain, fever, jaundice), biochemical abnormalities (raised serum aminotransferases, alkaline phosphatase, or gamma-glutamyl transpeptidase)

Prat 1996 (Continued)

more than twice the normal value, serum bilirubin above 50 (micromol/L), and morphological features (common bile duct dilated to more than 8 mm in patients with the gallbladder in situ and 10 mm in patients with previous cholecystectomy, or the presence of a hyperechoic image in the common bile duct).

2. Endoscopic treatment would be chosen for the treatment of the stones

Exclusion criteria

1. Patients younger than 50 who had not had cholecystectomy

2. Patients who declined to take part

Setting: secondary care (Gastroenterology Department, France)

Index tests	Index test: endoscopic ultrasound Technical specifications: GIF-EUM20; Olympus; 7.5 and 12 MHz probe Performed by: one of two experts in EUS Criteria for positive diagnosis: not stated
Target condition and reference standard(s)	Target condition: common bile duct stones Reference standard: attempted endoscopic extraction of stones in all patients Technical specifications: not applicable Performed by: endoscopists and surgeons Criteria for positive diagnosis: presence or absence of stones during endoscopic clearance
Flow and timing	Number of indeterminates for whom the results of reference standard was available: 1 (0.8%) Number of patients who were excluded from the analysis: 1 (0.8%)
Comparative	
Notes	

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
		High	High
DOMAIN 2: Index Test EUS			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
		High	High
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowl-	Yes		

Prat 1996 (Continued)
 edge of the results of the index tests?

	Low	Low
DOMAIN 4: Flow and Timing		
Was there an appropriate interval between index test and reference standard?	Yes	
Did all patients receive the same reference standard?	Yes	
Were all patients included in the analysis?	No	
High		

EUS: endoscopic ultrasound.

MRCP: magnetic resonance cholangiopancreatography.

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Adamek 1998	Not enough data for 2 x 2 table
Agapov 2006	Review of literature
Ahn 1998	Inappropriate reference standard
Ainsworth 2003	Not enough data for 2 x 2 table
Al-Jiffry 2010	Inappropriate reference standard
Alcaraz 2000	Inappropriate reference standard
Alhayaf 2008	Inappropriate reference standard
Aljebreen 2008	Inappropriate reference standard
Amouyal 1994	Inappropriate reference standard
Anderloni 2012	Not enough data for 2 x 2 table
Anderloni 2012a	Not enough data for 2 x 2 table
Ang 2007	Inappropriate reference standard
Ang 2007a	Inappropriate reference standard
Aube 2005	Inappropriate reference standard
Aubertin 1996	Inappropriate reference standard

Study	Reason for exclusion
Aubertin 1996a	Inappropriate reference standard
Basile 2000	Inappropriate reference standard
Becker 1997	Inappropriate reference standard
Berdah 2001	Inappropriate reference standard
Bhatt 2005	Not enough data for 2 x 2 table
Bilgin 2012	Inappropriate reference standard
Boboev 2012	Inappropriate reference standard
Bodula 2011	Inappropriate reference standard
Bokobza 1988	Review article
Boraschi 1999	Inappropriate reference standard
Brisbois 2001	Inappropriate reference standard
Calle 2006	Inappropriate reference standard
Calvo 2002	Inappropriate reference standard
Canto 1995	Not enough data for 2 x 2 table
Catalano 2000	Inappropriate reference standard
Cervi 2000	Inappropriate reference standard
Chak 1999	Inappropriate index test
Chan 1996	Not enough data for 2 x 2 table
Chan 2010	Inappropriate reference standard
Chandra 2010	Not enough data for 2 x 2 table
Chavez-Valencia 2009	Inappropriate reference standard
Chen 2003	Inappropriate reference standard
Chen 2012	Editorial
Chowdhury 1999	Inappropriate reference standard
Coakley 2002	Review article
Contractor 2004	Inappropriate reference standard
Dalton 2005	Inappropriate reference standard
Danaci 2002	Inappropriate reference standard

Study	Reason for exclusion
Dancygier 1995	Not enough data for 2 x 2 table
De Waele 2007	Inappropriate reference standard
del Pozo 2011	Not enough data for 2 x 2 table
Demartines 2000	Inappropriate reference standard
Denis 1993	Inappropriate reference standard
Derodra 1986	Letter to editor
Di Angelo 2010	Not enough data for 2 x 2 table
Di Angelo 2011	Not enough data for 2 x 2 table
Dittrick 2005	Inappropriate reference standard
Duchmann 1999	Not enough data for 2 x 2 table
Dwerryhouse 1998	Inappropriate reference standard
Eshghi 2008	Inappropriate reference standard
Familiari 2004	Inappropriate reference standard
Fernandez 2001	Inappropriate reference standard
Filippone 2003	Inappropriate reference standard
Galvao 2007	Inappropriate reference standard
Griffin 2003	Inappropriate reference standard
Gul 2010	Inappropriate reference standard
Gupta 2008	Inappropriate reference standard
Hasan 2010	Inappropriate reference standard
Hayashi 2002	Not enough data for 2 x 2 table
Ho 1999	Inappropriate reference standard
Hochwald 1998	Inappropriate reference standard
Holzknecht 1998	Inappropriate reference standard
Hrabar 2009	Inappropriate reference standard
Hussein 2002	Inappropriate reference standard
Isomoto 1998	Inappropriate reference standard
Ito 2001	Inappropriate reference standard

Study	Reason for exclusion
Janssen 2008	Not enough data for 2 x 2 table
Karakan 2009	Inappropriate reference standard
Kats 2003	Inappropriate reference standard
Kausar 2005	Not enough data for 2 x 2 table
Ke 2004	Inappropriate reference standard
Kejriwal 2004	Inappropriate reference standard
Kim 2002	Inappropriate reference standard
Kim 2005	Inappropriate reference standard
Kohut 2003	Not enough data for 2 x 2 table
Kondo 2005	Inappropriate reference standard
Lachter 2000	Inappropriate reference standard
Laghi 1998	Inappropriate reference standard
Laokpessi 2001	Inappropriate reference standard
Le Rhun 1999	Inappropriate reference standard
Lee 1996	Inappropriate reference standard
Lee 2010	Inappropriate reference standard
Leytens 2001	Inappropriate reference standard
Liessi 1996	Inappropriate reference standard
Lim 2003	Inappropriate reference standard
Liu 1999	Inappropriate reference standard
Liu 2005	Inappropriate reference standard
Lomanto 1997	Inappropriate reference standard
Lomas 1999	Inappropriate reference standard
Lundorf 2000	Inappropriate reference standard
Magnuson 1997	Inappropriate reference standard
Magnuson 1999	Inappropriate reference standard
Makary 2005	Inappropriate reference standard
Maurea 2009	Not enough data for 2 x 2 table

Study	Reason for exclusion
Meduri 1998	Inappropriate reference standard
Mendler 1998	Inappropriate reference standard
Meroni 2004	Inappropriate reference standard
Miao 2008	Not enough data for 2 x 2 table
Mirbagheri 2005	Inappropriate reference standard
Mofidi 2008	Inappropriate reference standard
Moon 2005	Inappropriate reference standard
Moreira 2006	Inappropriate reference standard
Morris-Stiff 2009	Inappropriate reference standard
Munir 2004	Inappropriate reference standard
Musella 1998	Inappropriate reference standard
Nandalur 2008	Inappropriate reference standard
Nau 2011	Inappropriate reference standard
Nebiker 2009	Inappropriate reference standard
Neri 2000	Inappropriate reference standard
Norero 2008	Inappropriate reference standard
Okaniwa 2002	Inappropriate reference standard
Palazzo 1995	Inappropriate reference standard
Palazzo 1998	Overview article
Palmucci 2010	Inappropriate reference standard
Pamos 1998	Inappropriate reference standard
Pamos 2003	Inappropriate reference standard
Pavone 1996	Inappropriate reference standard
Pavone 1996a	Inappropriate reference standard
Pavone 1996b	Inappropriate reference standard
Pavone 1997	Inappropriate reference standard
Pavone 1997a	Not enough data for 2 x 2 table
Polkowski 2001	Not enough data for 2 x 2 table

Study	Reason for exclusion
Pomakov 2007	Inappropriate reference standard
Pozo 2010	Not enough data for 2 x 2 table
Pulpeiro 2000	Inappropriate reference standard
Puri 2012	Not enough data for 2 x 2 table
Rahman 2010	Inappropriate reference standard
Regan 1996	Inappropriate reference standard
Regan 1996a	Not enough data for 2 x 2 table
Regan 1998	Inappropriate reference standard
Reinhold 1998	Inappropriate reference standard
Roig 1995	Not enough data for 2 x 2 table
Roig 1995a	Not enough data for 2 x 2 table
Rudowicz-Pietruszewska 2002	Inappropriate reference standard
Sabbagh 2000	Not enough data for 2 x 2 table
Sajewicz 2006	Inappropriate reference standard
Sakai 2007	Not enough data for 2 x 2 table
Salmeron 1994	Inappropriate reference standard
Saruc 2001	Inappropriate reference standard
Scaffidi 2009	Inappropriate reference standard
Scheiman 2001	Inappropriate reference standard
Schmidt 2012	Inappropriate reference standard
Seifert 2004	Inadequate index test
Shafiq 2003	Not enough data for 2 x 2 table
Shamiyeh 2005	Inappropriate reference standard
Shanmugam 2005	Inappropriate reference standard
Shim 1995	Inappropriate reference standard
Simeone 1997	Inappropriate reference standard
Skorka 1982	Inappropriate reference standard
Soto 1996	Inappropriate reference standard

Study	Reason for exclusion
Soto 2000	Inappropriate reference standard
Soto 2000a	Inappropriate reference standard
Sotoudehmanesh 2007	Not enough data for 2 x 2 table
Sperlongano 2005	Not enough data for 2 x 2 table
Srinivasa 2010	Inappropriate reference standard
Stevens 1996	Inappropriate reference standard
Stiris 2000	Inappropriate reference standard
Sugiyama 1997	Inappropriate reference standard
Sugiyama 1998	Inappropriate reference standard
Sverrisson 2012	Not enough data for 2 x 2 table
Taylor 2002	Inappropriate reference standard
Tennoe 1999	Inappropriate reference standard
Topal 2003	Inappropriate reference standard
Tripathi 2002	Inappropriate reference standard
Uehara 1998	Inappropriate reference standard
Urban 2002	Inappropriate reference standard
Vaishali 2004	Inappropriate reference standard
Valji 1996	Inappropriate reference standard
Varghese 1999	Inappropriate reference standard
Varghese 2000	Inappropriate reference standard
Vazquez-Sequeiros 2005	Inappropriate reference standard
Vazquez-Sequeiros 2011	Inappropriate reference standard
Verma 2006	Systematic review
Watanabe 2003	Inappropriate reference standard
Wehrmann 2009	Inappropriate reference standard
Wierzbicka-Paczos 1999	Not enough data for 2 x 2 table
Wong 2012	Inappropriate reference standard
Zaheer 2011	Not enough data for 2 x 2 table

Study	Reason for exclusion
Zaydan 2009	Inappropriate reference standard
Zhang 2012	Inappropriate reference standard
Zhi 2002	Not enough data for 2 x 2 table
Zidi 1997	Not enough data for 2 x 2 table
Zidi 1999	Inappropriate reference standard

DATA

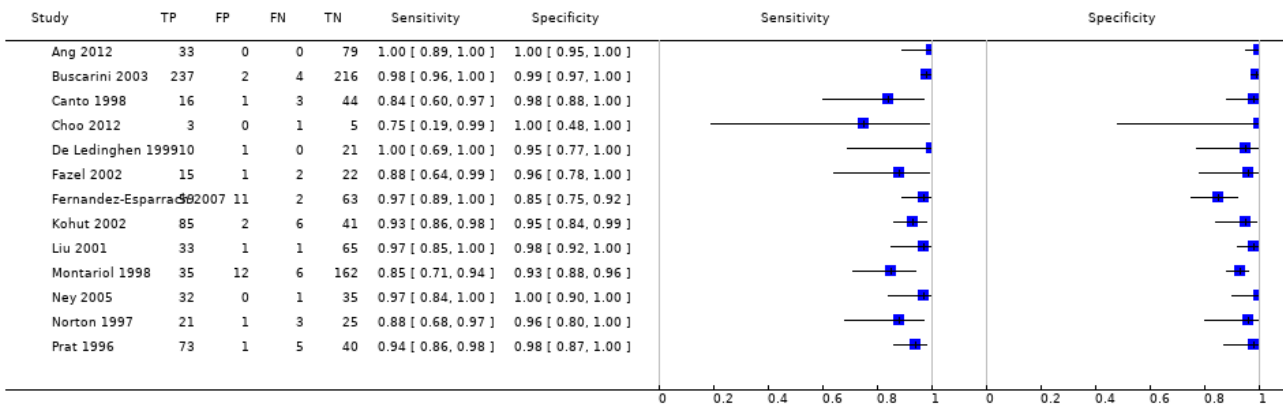
Presented below are all the data for all of the tests entered into the review.

Table Tests. Data tables by test

Test	No. of studies	No. of participants
1 Endoscopic ultrasound	13	1537
2 Magnetic resonance cholangiopancreatography	7	996

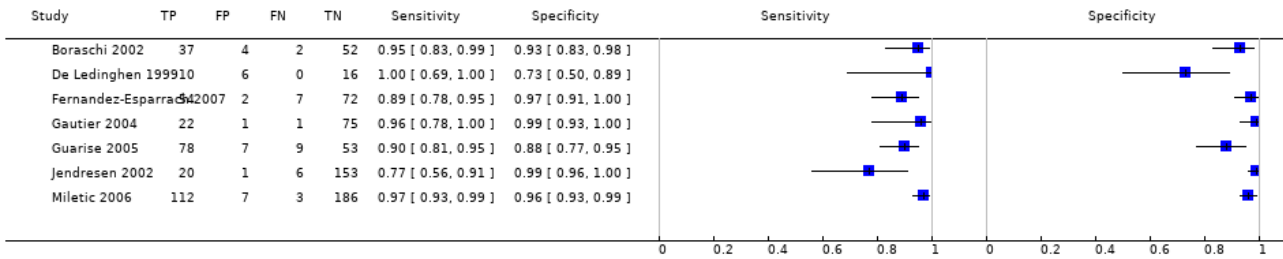
Test 1. Endoscopic ultrasound.

Review: Endoscopic ultrasound versus magnetic resonance cholangiopancreatography for common bile duct stones
Test: 1 Endoscopic ultrasound



Test 2. Magnetic resonance cholangiopancreatography.

Review: Endoscopic ultrasound versus magnetic resonance cholangiopancreatography for common bile duct stones
Test: 2 Magnetic resonance cholangiopancreatography



ADDITIONAL TABLES

Table 1. Application of the QUADAS-2 tool for assessing methodological quality of included studies

Domain 1: Patient sampling	Signalling question	Signalling question	Signalling question	Risk of bias	Concerns for applicability
Patient sampling	Was a consecutive or random sample of patients enrolled?	Was a case-control design avoided?	Did the study avoid inappropriate exclusions?	Could the selection of patients have introduced bias?	Were there concerns that the included patients and setting did not match the review question?
	<p>Yes: all consecutive patients or random sample of patients with suspected common bile duct stones were enrolled</p> <p>No: selected patients were enrolled</p> <p>Unclear: this was not clear from the report</p>	<p>Yes: case-control design was avoided.</p> <p>No: case-control design was not avoided</p> <p>Unclear: this was not clear from the report.</p>	<p>Yes: the study avoided inappropriate exclusions (i.e., difficult to diagnose patients)</p> <p>No: the study excluded patients inappropriately</p> <p>Unclear: this was not clear from the report</p>	<p>Low risk: 'yes' for all signalling questions</p> <p>High risk: 'no' or 'unclear' for at least one signalling question</p>	<p>Low concern: the selected patients represent the patients in whom the tests will be used in clinical practice (please see diagnostic pathway (Figure 1))</p> <p>High concern: there was high concern that patient selection was performed in a such a way that the included patients did not represent the patients in whom the tests will be used in clinical practice</p>
Domain 2: Index test					
Index test(s)	Were the index test results interpreted without knowledge of the results of the reference standard?	If a threshold was used, was it pre-specified?		Could the conduct or interpretation of the index test have introduced bias?	Were there concerns that the index test, its conduct, or interpretation differ from the review question?
	Yes: index test results were interpreted without knowl-	Not applicable		Low risk: 'yes' for all sig-	High concern: there was high concern that the conduct or interpreta-

Table 1. Application of the QUADAS-2 tool for assessing methodological quality of included studies (Continued)

	edge of the results of the reference standard		nalling questions	tion of the index test differs from the way it is likely to be used in clinical practice
	No: index test results were interpreted with knowledge of the results of the reference standard		High risk: 'no' or 'unclear' for at least one of the two signalling questions	Low concern: there was low concern that the conduct or interpretation of the index test differs from the way it is likely to be used in clinical practice
	Unclear: this was not clear from the report			
Domain 3: Reference standard				
Target condition and reference standard(s)	Was the reference standard likely to correctly classify the target condition?	Were the reference standard results interpreted without knowledge of the results of the index tests?	Could the reference standard, its conduct, or its interpretation have introduced bias?	Were there concerns that the target condition as defined by the reference standard does not match the review question?
	<p>Yes: all patients underwent the acceptable reference standard</p> <p>No: if all patients did not undergo an acceptable reference standard. Such studies will be excluded from the review</p> <p>Unclear: if the reference standard that the patients underwent was not stated. Such studies will be excluded from the review</p>	<p>Yes: reference standard results were interpreted without knowledge of the results of the index test</p> <p>No: reference standard results were interpreted with the knowledge of the results of the index test</p> <p>Unclear: this was not clear from the report</p>	<p>Low risk: 'yes' for all signalling questions</p> <p>High risk: 'no' or 'unclear' for at least one of the two signalling questions</p>	<p>Low concern: patients underwent endoscopic or surgical exploration for common bile duct stone</p> <p>High concern: all patients did not undergo endoscopic or surgical exploration for common bile duct stone</p>
Domain 4: Flow and timing				
Flow and timing	Was there an appropriate interval between index test and reference standard?	Did all patients receive the same reference standard?	Were all patients included in the analysis?	Could the patient flow have introduced bias?
	<p>Yes: the interval between index test and reference standard was shorter than or equal to four weeks (arbitrary choice)</p> <p>No: the interval between index test and reference stan-</p>	<p>Yes: all patients underwent endoscopic or surgical exploration for common bile duct stone irrespective of the index test results</p>	<p>Yes: all patients meeting the selection criteria (selected patients) were included in the analysis,</p>	<p>Low risk: 'yes' for all signalling questions</p> <p>High risk: 'no' or 'unclear' for at least</p>

Table 1. Application of the QUADAS-2 tool for assessing methodological quality of included studies (Continued)

dard was longer than four weeks Unclear: this was not clear from the report	No: patients underwent endoscopic or surgical exploration if the index test results were positive and underwent clinical follow-up for at least 6 months if the index test results were negative Unclear: this was not clear from the report. Such studies were excluded	or data on all the selected patients were available so that a 2 x 2 table including all selected patients could be constructed No: not all patients meeting the selection criteria were included in the analysis or the 2 x 2 table could not be constructed using data on all selected patients Unclear: this was not clear from the report	one signalling question
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APPENDICES

Appendix 1. Search strategies

Database	Period of Search	Search Strategy
MEDLINE (PubMed)	1946 until September 2012	(((bile duct[tiab] or biliary[tiab] OR CBD[tiab]) AND (stone[tiab] OR stones[tiab] OR calculus[tiab] OR calculi[tiab])) OR choledocholithiasis[tiab] OR cholelithiasis[tiab] OR "Choledocholithiasis"[Mesh] OR "Common Bile Duct Calculi"[MESH] OR "Cholelithiasis "[MESH]) AND (CT[tiab] OR tomodensitometry[tiab] OR MRI[tiab] OR NMRI[tiab] OR zeugmatogra*[tiab] OR ((computed[tiab] OR computerised[tiab] OR computerized[tiab] OR magneti*[tiab] OR MR[tiab] OR NMR[tiab] OR proton[tiab]) AND (tomogra*[tiab] OR scan[tiab] OR scans[tiab] OR imaging[tiab] OR cholangiogra*[tiab])) OR "Tomography, X-Ray Computed"[Mesh] OR "Magnetic Resonance Imaging"[Mesh] OR echogra*[tiab] OR ultrason*[tiab] OR ultrasound[tiab] OR EUS[tiab] OR "Ultrasonography"[Mesh] OR "Endosonography"[Mesh] OR cholangiogra*[tiab] OR cholangio?pancreatogra*[tiab] OR cholangiosco*[tiab] OR choledochosco*[tiab] OR ERCP[tiab] OR MRCP[tiab] OR "Cholangiography"[Mesh] OR "Cholangiopancreatography, Magnetic Resonance"[Mesh] OR liver function test[tiab] OR liver function tests[tiab] OR "Liver Function Tests"[Mesh])
EMBASE (OvidSP)	1947 until September 2012	1. (((bile duct or biliary or CBD) adj5 (stone or stones or calculus or calculi)) or choledocholithiasis or cholelithiasis).tw. 2. exp common bile duct stone/ or exp bile duct stone/ or exp cholelithiasis/ 3. 1 or 2

(Continued)

4. (CT or tomodesitometry or MRI or NMRI or zeugmatogra* or ((computed or computerised or computerized or magneti* or MR or NMR or proton) adj5 (tomogra* or scan or scans or imaging or cholangiogra*))).tw.
5. exp computer assisted tomography/
6. exp nuclear magnetic resonance imaging/
7. (echogra* or ultrason* or ultrasound or EUS).tw.
8. exp ultrasound/
9. (cholangiogra* or cholangio?pancreatogra* or cholangiosco* or choledochosco* or ERCP or MRCP).tw.
10. exp cholangiography/
11. (liver function test or liver function tests).tw.
12. exp liver function test/
13. 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12
14. 3 and 13

Science Citation Index Expanded (ISI Web of Knowledge)	1898 until September 2012	#1 TS=(((bile duct or biliary OR CBD) AND (stone OR stones OR calculus OR calculi)) OR choledocholithiasis OR cholelithiasis) #2 TS=(CT OR tomodesitometry OR MRI OR NMRI OR zeugmatogra* OR ((computed OR computerised OR computerized OR magneti* OR MR OR NMR OR proton) AND (tomogra* OR scan OR scans OR imaging OR cholangiogra*))) #3 TS=(echogra* OR ultrason* OR ultrasound OR EUS) #4 TS=(cholangiogra* OR cholangio?pancreatogra* OR cholangiosco* OR choledochosco* OR ERCP OR MRCP) #5 TS=(liver function test OR liver function tests) #6 #5 OR #4 OR #3 OR #2 #7 #1 AND #6
BIOSIS (ISI Web of Knowledge)	1969 until September 2012	#1 TS=(((bile duct or biliary OR CBD) AND (stone OR stones OR calculus OR calculi)) OR choledocholithiasis OR cholelithiasis) #2 TS=(CT OR tomodesitometry OR MRI OR NMRI OR zeugmatogra* OR ((computed OR computerised OR computerized OR magneti* OR MR OR NMR OR proton) AND (tomogra* OR scan OR scans OR imaging OR cholangiogra*))) #3 TS=(echogra* OR ultrason* OR ultrasound OR EUS) #4 TS=(cholangiogra* OR cholangio?pancreatogra* OR cholangiosco* OR choledochosco* OR ERCP OR MRCP) #5 TS=(liver function test OR liver function tests) #6 #5 OR #4 OR #3 OR #2 #7 #1 AND #6
Clinicaltrials.gov	September 2012	(bile duct) OR CBD OR choledocholithiasis OR cholelithiasis
Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA) in The Cochrane Library (Wiley)	September 2012	#1 (((bile duct or biliary or CBD) NEAR/5 (stone OR stones OR calculus OR calculi)) OR choledocholithiasis OR cholelithiasis):ti,ab,kw #2 MeSH descriptor Choledocholithiasis explode all trees #3 (#1 OR #2) #4 (CT OR tomodesitometry OR MRI OR NMRI OR zeugmatogra* OR ((computed OR computerised OR computerized OR magneti* OR MR OR NMR

(Continued)

OR proton) NEAR/5 (tomogra* OR scan OR scans OR imaging OR cholangiogra*)):ti,ab,kw

#5 MeSH descriptor Tomography, X-Ray Computed explode all trees

#6 MeSH descriptor Magnetic Resonance Imaging explode all trees

#7 (echogra* OR ultrason* OR ultrasound OR EUS):ti,ab,kw

#8 MeSH descriptor Ultrasonography explode all trees

#9 MeSH descriptor Endosonography explode all trees

#10 (cholangiogra* OR cholangio?pancreatogra* OR cholangiosco* OR choledochosco* OR ERCP OR MRCP):ti,ab,kw

#11 MeSH descriptor Cholangiography explode all trees

#12 MeSH descriptor Cholangiopancreatography, Magnetic Resonance explode all trees

#13 (liver function test OR liver function tests):ti,ab,kw

#14 MeSH descriptor Liver Function Tests explode all trees

#15 (#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14)

#16 (#3 AND #15)

Medion (www.medion-database.nl/)

September 2012

We will conduct four separate searches of the abstract using the terms:

bile duct

CBD

choledocholithiasis

cholelithiasis

ARIF (www.birmingham.ac.uk/research/activity/mds/projects/HaPS/PHEB/ARIF/databases/index.aspx)

September 2012

(bile duct) OR CBD OR choledocholithiasis OR cholelithiasis

CONTRIBUTIONS OF AUTHORS

KSG designed the search strategies. VG wrote the first draft review. VG, GP and DH independently evaluated references for inclusion in this review. VG and KSG independently extracted data from included studies and assessed the methodological quality of included studies. YT and KSG performed the analysis, critically commented on the interpretation of the results, and revised sections of the review. DS and BRD critically commented on the review.

DECLARATIONS OF INTEREST

Vanja Giljaca: none.

Kurinchi S Gurusamy: none.

David Higgle: none.

Goran Poropat: none.

Davor Stimac is a co-author in one of included studies ([Miletic 2006](#)). Davor Stimac is not affiliated with Shimadzu, Siemens, or Olympus.

Brian R Davidson: none.

Yemisi Takwoingi: none.

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Internal sources

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- National Institute of Health Research, UK.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

1. We used the statistical package Stata instead of SAS to fit the bivariate models.
2. We performed one main analysis. In this analysis indeterminate test results were excluded. The planned sensitivity analyses were considered inappropriate because of sparse data.
3. Author order changed: Vanja Giljaca, Kurinchi Selvan Gurusamy, Yemisi Takwoingi, David Higgie, Goran Poropat, Davor Stimac, Brian R Davidson.

NOTES

This review is based on a common protocol which needed to be split in to three reviews ([Giljaca 2013](#)).

INDEX TERMS

Medical Subject Headings (MeSH)

*Cholangiopancreatography, Magnetic Resonance [standards]; *Endosonography [standards]; Choledocholithiasis [*diagnosis] [*diagnostic imaging]; Sensitivity and Specificity

MeSH check words

Humans