Appendix G: Included studies

G.1 Included studies question 1

Table 1: Wegge (1985)

Patient characteristics	**Population:** 192 emergency cases admitted for the following criteria: upper abdominal pain less than a week in duration, no previous diagnosis of gallstones, capable of giving informed consent and an interview, not previously admitted to the study. **Mean age:** Not stated **Males/females:** Not stated **Country:** Denmark **Other comments:** Unclear how the presence or absence of gallstones was determined.
Prognostic factor(s)	The study aimed to evaluate the frequency of 'text book' symptoms and signs of gallstones in patients admitted with abdominal pain as emergency patients A structured interview and standardised physical examination were carried out, the details of which were condensed into 37 prognostic factors for investigation covering demographic information (gender, age, menopause, parity, family history), present and previous symptoms, and clinical signs on admission. Factors that were significantly different in univariate analyses were entered into a multivariate regression
Length of follow up	Not stated
Results	

Factor	People with gallstones n=49	People without gallstones n=143	Significant in univariate analyses	Significant in multivariate analyses
Age >50 years	67%	47%	Yes	No
Previous attacks of similar pain	80%	55%	Yes	No
Previous intolerance to fatty foods	49%	18%	Yes	No
Current receipt of analgetic injections at home	39%	13%	Yes	No
Current radiation of pain to back or shoulder	63%	36%	Yes	No
Tenderness in upper right quadrant on admission	67%	38%	Yes	No

NB Authors do not report data in relation to the analyses they conducted

Summary	There were no significant predictors of gallstones in patients admitted with abdominal pain

G.2 Included studies question 2

Ahmed & Diggory (2011)

Patient characteristics	**Population:** Retrospective review of patients undergoing laparoscopic cholecystectomy for symptoms related to gallstone disease between 2005 and 2008 **Number of patients included:** 1869 (an additional 231 patients were available for analysis but were excluded due to the presence of open gallbladder specimens sent to histology) **Number of patients excluded:** Not stated **Mean age:** Not stated **Males/females:** Not stated **Country:** UK **Other comments:** None
Reference standard	**Reference standard:** Surgery **Details:** Laparoscopic cholecystectomy with post operative histopathology **Number unable to participate in the reference test :** Not stated
Index test(s)	**(1) Ultrasound** **Test:** Ultrasound scans were performed by a combination of radiologists and ultrasonographers throughout the trust. No details of equipment used are provided. Histopathology specimens were reported by a range of consultant and specialist registrar pathologists. **Number unable to participate in the index test and reasons given:** Not stated
Results	**Ultrasound - Performed by either radiologist or ultrasonographer**

		Reference test		
		+	**-**	**Total**
Index test	**+**	1549 (TP)	274 (FP)	1823
	-	0 (FN)	46 (TN)	46
	Total	1549	320	1869

Sensitivity: 1.000 (95%CI: 1.000, 1.000); Specificity: 0.144 (95%CI: 0.104, 0.184)
LR+: 1.169 (95%CI: 1.118, 1.223); LR−: 0.002 (95%CI: 0.000, 0.036)

Ultrasound - Performed by radiologist only

		Reference test		
		+	**-**	**Total**
Index test	**+**	534 (TP)	99 (FP)	633
	-	0 (FN)	16 (TN)	16
	Total	534	115	649

Sensitivity: 1.000 (95%CI: 0.999, 1.000); Specificity: 0.139 (95%CI: 0.072, 0.207)
LR+: 1.165 (95%CI: 1.081, 1.254); LR−: 0.007 (95%CI: 0.000, 0.109)

Ultrasound - Performed by ultrasonographer only

		Reference test		
		+	**-**	**Total**
Index test	**+**	986 (TP)	205 (FP)	1191
	-	0 (FN)	29 (TN)	29
	Total	986	234	1220

Sensitivity: 1.000 (95%CI: 0.999, 1.000); Specificity: 0.124 (95%CI: 0.080, 0.168)
LR+: 1.143 (95%CI: 1.089, 1.200); LR−: 0.004 (95%CI: 0.000, 0.066)

Alponat (1997)

Patient characteristics

Population: Consecutive patients who were undergoing open or laparoscopic cholecystectomy between July 1991 and July 1996 and had an indication for ERCP for the following reasons: LFT elevation (present or previous), Pancreatitis (present or previous), Jaundice (present or previous), Cholangitis, Dilated CBD without stone on ultrasound, Dialated CBD with stone on ultrasound.

Number of patients included: 878

Number of patients excluded: 684 patients undergoing cholecystectomy were excluded because they didn't have an indication for ERCP and therefore did not undergo the test

Mean age: 52 years (range= 13 to 86)

Males/females: 73 males, 121 females

Country: Singapore

Other comments:

Reference standard

Reference standard: Pre or post operative ERCP

Details: Performed with an Olympus JFIT side viewing duodenoscope under fluoroscopic control. If sphincterotomy was indicated, the bile duct was cannulated with a papillotome; a combination of coagulation and cutting diathermy was used. Stones were extracted using a Dormia basket or balloon catheter. Cholecystectomy was done 24 to 72 hrs after ERCP

Number unable to participate in the reference test: 2 patients were excluded because CBD cannualtion failed and were excluded from the study

Prognostic factors

The following factors were analysed for predicting CBDS: age, sex, history of right hypochondrial pain, indication for procedure- previous or present elevated serum liver enzymes, clinical findings of cholangitis, jaundice, pancreatitis, dilated CBD over 6mm with or without stone on ultrasound, serum level of each liver enzyme (AST,ALT, ALP, GGT,LDH) bilirubin and ultrasonographic findings.

Age was categorised as young (under 65 years) and old (65 years and above). Biochemical analysis of blood was evaluated as abnormal when liver enzymes and bilirubin levels were greater than 2 times normal. Elevated liver enzyme tests were considered present when any three of AST, ALT, ALP, GGT and LDH were elevated.

The following factors were significant in in univariate analysis and were entered into the multiple logistic regression: RUQ pain, Cholangitis, Resolved pancreatitis, Jaundice-previous, Elevation of liver enzymes-present, Pancreatitis-present, Aspartate transaminase, Alanine transaminase, Alkaline phosphatase, Gamma glutamyl transpeptidase, GB stone >1, GB stone size >1cm

Results

Prognostic factor	With CBDS (n=62)	Without CBDS (n=130)	Effect size (95% confidence interval)
Cholangitis	6	2	OR=5.30 (CI= 1.55 to 71.79)
CBD>6mm with stone on US	26	10	OR=2.90 (CI= 2.85 to 18.99)
AST	55	78	OR=7.40 (CI= 1.25 to 5.88)
Conjugated bilirubin	42	28	OR=10.50 (CI= 2.35 to 11.83)

Altun et al. (2007)

Patient characteristics

Population: Retrospective review of all patients with histopathologically proved cholecystitis who had undergone abdominal MR examinations within 1 month before surgery. All MR examinations were performed for abdominal pain and problem solving within 1 month prior to surgery.

Number of patients included: 32

Number of patients excluded: Not stated

Mean age: Acute cholecystitis= 65 years (SD= 17)

Chronic cholecystitis= 41 years (SD= 15)

Males/females: Acute cholecystitis= 14 males, 5 females

Chronic cholecystitis= 1 male, 12 females

Country: Unclear- Probably USA but could be Brazil

Other comments: Researchers were from USA and Brazil, study states it was in compliance with HIPAA (USA health insurance act), researcher(s) were funded by The Council of Scientific and Technological Development Brasil.

Reference standard

Reference standard: Surgery

Details: Histopathologically proved cholecystitis

Number unable to participate in the reference test : None

Index test(s)

(1) MRI

Test: MR imaging of the upper abdomen with 1.5T MR systems (Vision, Sonata or Avanto) using a phased array torso coil. MR imaging was performed using a breathing dependent or breathing independent protocol depending on the patients ability to suspend respiration. All patients had gadodiamide intravenously in a power injected bolus.

MR results were independently and retropsectively interpreted by two radiologists who were blind to the clinical information but aware that cholecystitis was present

Number unable to participate in the index test and reasons given: None, but in 28 patients with normal renal function, increased contrast enhnacement of the gallbaldder wall was evaluated on post contrast delayed interstitial-phase images by comparing with the renal parenchymal enhancement. Increased gallbladder wall enhancement was accepted as positive for acute cholecystitis when it was equal to or greater than the renal parenchymal enhancement qualitively. In 4 patinets with chronic renal failure gallbladder wall enhancement was evaluated soley on the reviewer's experiences.

Results

MRI

		Reference test		
		+	**-**	**Total**
Index test	**+**	18 (TP)	4 (FP)	22
	-	1 (FN)	9 (TN)	10
	Total	19	13	32

Sensitivity: 0.947 (95%CI: 0.821, 1.000); Specificity: 0.692 (95%CI: 0.403, 0.982)

LR+: 3.079 (95%CI: 1.353, 7.007); LR−: 0.076 (95%CI: 0.011, 0.530)

All patients in the analysis had either acute cholecystis (AC) or chronic cholecystitis (CC).

The results refer to the diagnosis of acute cholecystitis, and demonstrate the tests ability at differentiating between AC and CC

Barr (1999)

Patient characteristics	**Population:** Retrospective review of 134 consecutive patients who had undergone ERC prior to laparoscopic cholecystectomy. **Number of patients included:** 107 (57 with stones, 50 without stones) **Number of patients excluded:** 27 patients were excluded because there was evidence of common bile duct obstruction and positive indications for bile duct exploration such as ultrasound evidence, cholangitis, icterus, and fulminant pancreatitis, or because they had coexisting malignancies, were on anticonvulsants or enzyme inducers that markedly affect GGT levels, or were alcoholics. **Mean age:** Patients with stones mean age = 57.9 years (SD= 19.7) Patients without stones mean age= 53.8 years (SD= 19.1) **Males/females:** 44 males, 63 females **Country:** USA **Other comments:** The multivariate logistic regression was performed on the data from 76 patients who had all variables available for analysis. The diagnostic accuracy data (sensitivities & specificities) were validated on 36 patients, but it is unclear if these were from the study population or recruited elsewhere.
Reference standard	**Reference standard:** ERCP **Details:** All patients underwent ERC to ascertain the presence or absence of CBDS. All patients had documented cholelithiasis and subsequently underwent laparoscopic cholecystectomy **Number unable to participate in the reference test:** None
Prognostic factors	The following factors were analysed to predict CBDS: age, sex, admission temperature, weight, AST, ALT, ALP, GGT, bilirubin, amylase, lipase, current or recent medications, common bile duct diameter as measured by ultrasonography, ERC findings of the presence or absence of common bile duct stones. All patients had documented cholelithiasis and subsequently underwent cholelcystectomy For the multivariate regression it was unclear why some predictors were entered into the model and some were not. Researchers built two models, one containing GGT and one containing AP as they felt that GGT is not always available in hospitals and GGT and AP are similarly sensitive at detecting stones.
Results	

Model 1		ERCP	
		+	-
-3.15 + (0.0042 x GGT) + (0.29 x CBDIA) – (0.002 x AMY)	≥0	Not reported	Not reported
	<0	Not reported	Not reported

Sensitivity (0.87, CI= 0.6 to 0.98), Specificity (0.71, CI= 0.49 to 0.89)

Model 2		ERCP	
		+	-
-3.46 + (0.0081 x AP) + (0.35 X CBDIA) – (0.0019 X AMY)	≥0	Not reported	Not reported
	<0	Not reported	Not reported

Sensitivity (0.80, CI= 0.52 to 0.96), Specificity (0.71, CI= 0.48 to 0.89)

Chan et al. (1996)

Patient characteristics

Population: Patients with suspected choledocholithiais. These were hospital inpatients referred for endoscopy because of clinical evidence of right upper quadrant or epigastric pain, jaundice or dark coloured urine, fever, or biochemical jaundice.

10 patients had previously undergone sphincterotomy.

42 pathients had previously ungergone ultrasound

Number of patients included: 47

Number of patients excluded: -

Mean age: Mean= 65 years Range= 32 to 86 years

Males/females: 27 male, 20 female

Country: Hong Kong

Other comments: -

Reference standard

Reference standard: ERCP

Details: Performed as part of the standard ERCP procedure, and performed within 5 hours of the index test.

Images were seperately interpreted in a prospective, blinded fashion.

Clinical, laboratory, US and endoscopic findings were used by the investigators while reviewing ERC images

Number unable to participate in the reference test : 2 patients were unable to participate due to the procedure being unsuccessful (unclear why it was unsucessful)

Index test(s)

(1) MR cholangiography

Test: Examinations were performed with a 1.5-T magnet (Gyroscan) with a body coil. No special preparation was used. The patients were examined in supine position. A survey MR examination and a turbo spin echo T2 weighted axial MR examination of the upper abdomen were performed first. These images served as guides with which to determine the obliquity of the coronal oblique sections to be obtained at MR cholangiography. MR cholangiography was performed with a non breath hold, fat supressed respiratory triggered turbo spin echo sequence. 25 oblique coronal source images were aquired with a 3mm section thickness and a 0.7 - 1.0mm section overlap, covering a volume with a depth of 50-57.5mm. The following imaging parameters were used: repetition time 2,200-5,686msec and echo time 330msec (2,200-5,686/330), a 256 x 192 matric, a 34-37.5cm field of view, 6 signals acquired, and a turbo factor of 54. the data set from the source oblique coronal image was also reformatted using a standard MIP algorithm. The coronal oblique source images and the MIPs of the MR cholangiograms were analysed for duct abnormalities and stones, but the axial images of the upper abdomen were not.

Images were seperately interpreted in a prosepctive, blind fashion.

Name, age and sex were the only data available to the investigators reviewing MR images

Number unable to participate in the index test and reasons given: None

Results

All study participants

		Reference test		
		+	**-**	**Total**
Index test	**+**	1. 18 (TP)	2. 4 (FP)	3. 22
	-	4. 1 (FN)	5. 22 (TN)	6. 23
	Total	7. 19	8. 26	9. 45

Sensitivity: 0.947 (95%CI: 0.821, 1.000); Specificity: 0.846 (95%CI: 0.688, 1.000)

LR+: 6.158 (95%CI: 2.485, 15.262); LR−: 0.062 (95%CI: 0.009, 0.422)

De Vargas et al. (2006)

Patient characteristics	**Population:** Retrospective review of patients with acute cholecystitis who underwent imaging examinations between April 2003 and April 2004. Patients whose diagnostic examinations were performed at other sites were not available, patients who did not undergo emergency surgery due to contraindications, and patients whose operation was delayed for more than 48 hours after presentation were excluded. **Number of patients included:** 35 **Number of patients excluded:** None **Mean age:** 66.6 years (range= 27 to 99) **Males/females:** 23 males, 12 females **Country:** Italy **Other comments:** None
Reference standard	**Reference standard:** Surgery **Details:** All patients underwent surgical and histological examinaton. Patients with complicated cholecystitis were considered true positives, whereas those with non complicated disease (i.e. simple acute cholecystits, chronic cholecystic disease) were considered true negative **Number unable to participate in the reference test :** None
Index test(s)	**(1) CT** **Test:** CT spiral examinations were performed with a Siemens Somatom before and after an IV injection of contrast agent, with scans during the venous phase (60 to 70 second delay) without oral contrast agent. **Number unable to participate in the index test and reasons given:** In one case CT was performed without contrast agent due to alergy iodinated contrast agents. In addition to the parameters examined for US, with the exception of Murphy's sign, presence of free air and alterations to vascularisation of the liver parenchyma adjacent to the gallbladder were also evaluated. **(2) Ultrasound** **Test:** Ultrasound was performed using AU5 Esaote and Logic 400 scanners with 3.5 to 5 MHz probes. The parameters examined were: focal or diffuse wall thickening (more than 3mm), stratification or double parietal profile; distension (max transverse diameter greater than 5cm); stones in the gallbladder or biliary tract; sludge or endoluminal aggregates; parietal, endoluminal or extra-parietal gas collections; aerobilla; free or sacculated pericholecystic or abdominal fluid collections; intra and extra hepatic bilairy tract dilation; presence of ultrasonographic Murphy's sign; and possible associated findings. **Number unable to participate in the index test and reasons given:** None
Results	**CT** Sensitivity: 1.000 (95%CI: 0.944, 1.000); Specificity: 1.000 (95%CI: 0.833, 1.000) LR+: 7.600 (95%CI: 0.566, 101.986); LR−: 0.057 (95%CI: 0.004, 0.873)
	Ultrasound

		Reference test		
		+	**-**	**Total**
Index test	**+**	9 (TP)	0 (FP)	9
	-	0 (FN)	3 (TN)	3
	Total	9	3	12

		Reference test		
		+	**-**	**Total**
Index test	**+**	6 (TP)	0 (FP)	6
	-	10 (FN)	14 (TN)	24
	Total	16	14	30

Sensitivity: 0.375 (95%CI: 0.107, 0.643); Specificity: 1.000 (95%CI: 0.964, 1.000)
LR+: 11.471 (95%CI: 0.704, 187.012); LR−: 0.639 (95%CI: 0.434, 0.940)

Test distinguishes between complicated and uncomplicated cholecystitis.
Paper reports that specificity was 70% but calculations using the data the paper provides shows specificity to be 100%

Griffin et al. (2003)

Patient characteristics

Population: Consecutive patients with gallstones referred for ERCP prior to cholecystectomy over a 2 year period.

Patients were referred for ERCP because of abnormal LFTs (57 patients), current or recent jaundice (38 patients), Bile duct dilation greater than 20mm on ultrasound (20 patients)

Number of patients included: 133

Number of patients excluded: 18, 10 because they were unsuitable for MRCP due to claustrophobia or metal implants, and 8 because of failed ERCP

Mean age: 58 years (range= 18 to 89)

Males/females: 29 male, 86 female

Country: UK

Other comments: -

Reference standard

Reference standard: ERCP

Details: Two endoscopists performed ERCP by using a side viewing endoscope with video monitor display. Patients were placed in the left lateral position and sedated. Buscopan was administered routinely to reduce duodenal motility. Non ionic contrast agent was injected under fluroscopic control

Number unable to participate in the reference test : 8 patients were unable to participate due to technical difficulties

In addition 5 patients who completed the test developed post ERCP pancreatitis

Index test(s)

(1) MRCP

Test: MRCP was carried out on a Seimans Vision Scanner using a body array coil placed over the right upper quadrant of the abdomen. This allowed 10mm thick T2-weighted turbo spin echo (TSE) and T2-weighted half Fourier aquired single shot turbo spin echo (HASTE) scans to be aquired in the oblique-coronal plabe through the region of the majpr biliary and pancreatic ducts. These scans were followed by contiguous 4mm thick fat saturated TSE images in the axial plane through the extrahepatic ducts and pancreas.

Images were assessed by two consultant radiologists who were unaware of other imaging findings. The images were analysed for bile duct dilation, intraluminal filling defects and strictures. Stones were diagnosed by the presence of low signal or well defined rounded lesions within the duct lumen.

Number unable to participate in the index test and reasons given: 10 due to metal implants or claustrophobia

Results

MRCP

		Reference test		
		+	**-**	**Total**
Index test	**+**	31 (TP)	3 (FP)	34
	-	6 (FN)	75 (TN)	81
	Total	37	78	115

Sensitivity: 0.838 (95%CI: 0.706, 0.970); Specificity: 0.962 (95%CI: 0.912, 1.000)
LR+: 21.784 (95%CI: 7.117, 66.673); LR−: 0.169 (95%CI: 0.081, 0.351)

MRCP - Stones less than or equal to 5mm

		Reference test		
		+	**-**	**Total**
Index test	**+**	2 (TP)	0 (FP)	2
	-	5 (FN)	75 (TN)	80
	Total	7	75	82

Sensitivity: 0.286 (95%CI: 0.000, 0.692); Specificity: 1.000 (95%CI: 0.993, 1.000)
LR+: 47.500 (95%CI: 2.492, 905.423); LR−: 0.692 (95%CI: 0.434, 1.105)

MRCP - Stones greater than 5mm

		Reference test		
		+	**-**	**Total**
Index test	**+**	29 (TP)	3 (FP)	32
	-	1 (FN)	75 (TN)	76
	Total	30	78	108

Sensitivity: 0.967 (95%CI: 0.886, 1.000); Specificity: 0.962 (95%CI: 0.912, 1.000)
LR+: 25.133 (95%CI: 8.270, 76.386); LR−: 0.035 (95%CI: 0.005, 0.238)

Hakansson et al. (2000)

Patient characteristics	**Population:** Patients consulting the department of surgery for suspected acute choelcystitis who had undergone US and MR imaging within 24 hours between July 1997 and July 1998 **Number of patients included:** 94 **Number of patients excluded:** 59 because of no access to MR during office hours, overweight, unwilling to participate, non compliant with study **Mean age:** Not stated (Range= 17 to 87 years) **Males/females:** 18 males, 17 females **Country:** Sweden **Other comments:** None
Reference standard	**Reference standard:** Surgery **Details:** The final diagnosis of acute choelcystits was confirmed by findings of an inflamed gallbladder at surgery and/or followed by a positive histopathologic examination. **Number unable to participate in the reference test :** None, as patients were excluded earlier by the study protocol. Unclear if the 4 patients excluded because they were overweight was an exclusion for the reference standard or one of the index tests.
Index test(s)	**(1) Ultrasound** **Test:** Grey scale US equipment using either a 3.5 or 4 MHz probe (Acuson 128XP). Performed by 10 different radiologists. The US findings were registered as 1) gallbladder wall thickness greater than 3mm, 2) striations indicating wall oedema, 3) distension of the gallbladder with a diameter greater than 40mm, 4) pericholecystic fluid collection, 5) positive US Murphy's sign, 6) impacted stone of the gallbladder neck, 7) presence of stones in the gallbladder, 8) stones in the common bile ducts. One or more of criteria 1 to 6 indicated acute cholecystitis, Criteria 7 & 8 were auxiliary findings. **Number unable to participate in the index test and reasons given:** None, as patients were excluded earlier by the study protocol. Unclear if the 4 patients excluded because they were overweight was an exclusion for ultrasound or MR/Surgery.
	(2) MRCP **Test:** A 1.5 T system (Magnetom vision) was used. A circularly polarised phased array body coil was used. No contrast medium was administered. All patients received Buscopan to reduce motion artefacts from intestinal peristalsis. All sequences were aquired in breath hold. T1- weighted gradient echo (GE) and T2-weighted half-Fouriersingle shot turbo spin echo (HASTE) sequences were used to examine the liver and pancreas. T2-weighted turbo spin echo (TSE) with fat supression was used for examining the gallbladder. All pulse sequences were aquired in the axial plane. In addition 2 dedicated pulse sequences for MR cholangiopancreatography were aquired in oblique coroanl planes, 1) heavily T2W TSE with thick slab (70-90mm) with different angles through the region of the biliary tree; and 2) a fat supressed breath hold sequence with multiple thin slices angulated in order to avoid overlying bowel loops when visualising the bilairy tree. The outcome of the US examination was unknow to the MR operator and radiologist interpreting the images. MR findings were: 1) gallbladder wall thickness greather than 3mm, 2) gallbladder wall oedema, 3) distension of the gallbladder with a dimaeter greater than 40mm, 4) pericholecystic fluid collection. 5) fluid around the liver shaped like a C, 6) impacted stone in the gallbladder neck, 7) presence of stones in the gallbladder, 8) stones in the common bile duct. One or more criteria 1-6 indicated acute cholecystitis. Crietria 7 & 8 were auxiliary findings. **Number unable to participate in the index test and reasons given:** None, as

	patients were excluded earlier by the study protocol. Unclear if the 4 patients excluded because they were overweight was an exclusion for MRCP or US/Surgery.
Results	**Ultrasound** Sensitivity: 0.654 (95%CI: 0.452, 0.856); Specificity: 0.889 (95%CI: 0.628, 1.000) LR+: 5.885 (95%CI: 0.908, 38.140); LR−: 0.389 (95%CI: 0.219, 0.693)

		Reference test		
		+	**-**	**Total**
Index test	**+**	17 (TP)	1 (FP)	18
	-	9 (FN)	8 (TN)	17
	Total	26	9	35

	MRCP Sensitivity: 0.885 (95%CI: 0.743, 1.000); Specificity: 0.889 (95%CI: 0.628, 1.000) LR+: 7.962 (95%CI: 1.248, 50.790); LR−: 0.130 (95%CI: 0.044, 0.386)

		Reference test		
		+	**-**	**Total**
Index test	**+**	23 (TP)	1 (FP)	24
	-	3 (FN)	8 (TN)	11
	Total	26	9	35

Holzknecht et al. (1998)

Patient characteristics

Population: Patients who had an ERCP planned within the next 2 days. Patients with contraindications for MR were excluded

Number of patients included: 66

Number of patients excluded: 5 patients were excluded because of cardiac pacemaker (2) and ERCP failure (3)

Mean age: 55.8 years (SD= 17.9)

Range= 14 to 84

Males/females: 30 male, 31 female

Country: Germany

Other comments: -

Reference standard

Reference standard: ERCP

Details: ERCP was performed with the standard technique. Each of the endoscopists had over 10 years experience in performing ERCP. Only duct parts relevant for the suspected diagnosis were opacified with contrast material to reduce complications. Therefore MR findings in duct areas not opacified at ERCP were excluded.

Number unable to participate in the reference test : 3 because of prior gastric surgery (2) and failure of papilla intubation (1)

Index test(s)

(1) MRCP

Test: MR examinations were preformed on a 1.5T whole body system. Before cholangiography T1-weighted axial gradient-echo imaging was performed to localise the biliary system (repetition time 140msec, echo time 4.8msec, sequence fast low angle shot or FLASH, flip angel 70 degrees, 8mm section thickness, 18 sections in a 20 second breath hold). Two different techniques were applied: RARE and half-Fourier RARE. For the half-Fourier RARE imaging, the number of sections required was done in a single breath hold. For dyspneic patients, the number of sections was achieved through a series of shorter breath holds. RARE was performed with a section thickness of 60 to 80mm in the coronal orientation (echo spacing 11.5 msec, effective echo time 1,200msec, image matrix 240 x 256, field of view 300mm, spatial resolution 1.25 x 1.17mm). Half-Fourier RARE was performed with a 4mm section thickness (field of view 280 to 320mm, matrix 240 x 256, in plane resolution 1.17 to 1.33 x 1.09 to 1.25mm). Fifteen sections were aquired in a single breath hold. In dyspneic patients the number of sections acquired was reduced to 9 or 5 by using 18 or 10 second breath holds. Contrast medium or medication was not administed

Number unable to participate in the index test and reasons given: 2 patients with cardiac pacemakers

Results

MRCP - Consensus of 2 onsite radiographers

		Reference test		
		+	**-**	**Total**
Index test	**+**	12 (TP)	2 (FP)	14
	-	1 (FN)	46 (TN)	47
	Total	13	48	61

Sensitivity: 0.923 (95%CI: 0.740, 1.000); Specificity: 0.958 (95%CI: 0.891, 1.000)

LR+: 22.154 (95%CI: 5.653, 86.815); LR−: 0.080 (95%CI: 0.012, 0.528)

MRCP - One off site radiologist

		Reference test		
		+	**-**	**Total**
Index test	**+**	11 (TP)	3 (FP)	14
	-	2 (FN)	45 (TN)	47

	Total	13	48	61

Sensitivity: 0.846 (95%CI: 0.612, 1.000); Specificity: 0.938 (95%CI: 0.859, 1.000)
LR+: 13.538 (95%CI: 4.418, 41.489); LR−: 0.164 (95%CI: 0.046, 0.588)

Jovanovic et al. (2011)

Patient characteristics

Population: Consecutive patients who underwent ERCP after being referred for a firm clinical and/or biochemical suspicion of CBDS based on a typical combination of clinical and/or biochemical parameters

Number of patients included: 203

Number of patients excluded: Number not stated. Patients were excluded if they had prior cholecystectomy, history of finding of sclerosing cholangitis and any other disease or condition which can result in biochemical and/or songraphic markers of CBDS. Patients with clear clinical/biochemical signs of bacterial cholangitis and/or biliary pancreatitis were also excluded.

Mean age: Median= 63 years (interquartile range= 49 to 74)

Range= 19 to 90 years

Males/females: 66 male, 137 female

Country: Boznia and Herzegovina

Other comments: This study also provides prognostic data on biochemical and ultrasound data, but the multivariate analyis is poorly reported and cannot be meaningfully extracted.

Reference standard

Reference standard: ERCP

Details: ERCP was performed by one examiner who had more than 20 years experience performing the procedure with the Olympus TJF type 145 Exera endoscope

Number unable to participate in the reference test : None

Index test(s)

(1) Ultrasound

Test: Transcutaneous ultrasound was performed by one of 5 experienced examiners (>1000 procedures) with the GE Logic 400 using transducer calibrated on frequencies from 3.5 to 5 MHz with multiple focal spot. US examination was performed using the standard right oblique scan with appropriate modifications to conform to the patients' anatomical peculiarities. Dimensions of CBD were measured in its proximal, middle and interhepatic part, using mean value of three consecutive measurements of the widest part. As an upper limit the normal range of CBD diameter was taken with the value 7mm. The presence of hyperechogenic shadows.

Number unable to participate in the index test and reasons given: None

Results

Ultrasound - Dilated CBD>7mm or CBD stones on US

		Reference test		
		+	**-**	**Total**
Index test	**+**	89 (TP)	69 (FP)	158
	-	9 (FN)	36 (TN)	45
	Total	98	105	203

Sensitivity: 0.908 (95%CI: 0.846, 0.970);
Specificity: 0.343 (95%CI: 0.247, 0.438)
LR+: 1.382 (95%CI: 1.187, 1.609);
LR−: 0.268 (95%CI: 0.136, 0.527)

Ultrasound - Dilated CBD>7mm and CBD stones on US

		Reference test		
		+	**-**	**Total**
Index test	**+**	146 (TP)	12 (FP)	158
	-	32 (FN)	13 (TN)	45
	Total	178	25	203

Sensitivity: 0.820 (95%CI: 0.761, 0.879); Specificity: 0.520 (95%CI: 0.304, 0.736)
LR+: 1.709 (95%CI: 1.130, 2.585); LR−: 0.346 (95%CI: 0.212, 0.564)

Kondo et al. (2005)

Patient characteristics	**Population:** High suspicion of choledocholithiasis based on recent clinical symptoms (right upper quadrant abdominal pain, jaundice, fever) and biochemical abnormalities (elevated serum levels of transaminases, alkaline phosphatase, gamma glutamyl transpeptidase, or bilirubin), with or without abnormal findings on abdominal ultrasonography (high echoic spots in the common bile duct or bile duct dilation) **Number of patients included:** 176 **Number of patients excluded:** 146 due to: presentation of acute cholangitis (131), presentation of recurrent choledocholithiasis (9), Contraindications for diagnostic procedures (6) **Mean age:** 64 years (range= 38 to 93) **Males/females:** 16/12 **Country:** Japan **Other comments:** This study also presents diagnostic test accuracy data for EUS which was used as the index test compared to ERCP used as the reference standard. This has not been extracted as the GDG agreed that EUS and ERCP are both reference standards.
Reference standard	**Reference standard:** ERCP **Details:** Performed using a duodenal endoscope (Olympus JF-230 or JF-240). Conscious sedation was achieved with diazepam and pithidine hydrochlorode. Bowel movement was surpressed with scopolamine butylbromide or glucagon. Cholangiography was performed in the standard manner while not intending pancreatography. When no CBDS was detected with cholangiography, IDUS was performed to confirm the absence of stones. CBDS detected were removed with a stone basket, a balloon catheter, or both following endoscopic papillary balloon dilation. **Number unable to participate in the reference test :** Two patients refused to undergo ERCP because no stone had been detected by the three other examinations and each patient refused further investigation.
Index test(s)	**(1) MRCP** **Test:** 1.5R superconducting magnet (Magnetom Vision). Ferric ammonium citrate was administered orally as a negative contrast agent. The test was performed after a fast >4hrs to promote gallbladder filling and gastric emptying. Patients were examined in the supine position and a phased array coil was strapped around the abdomen. A T1 weighted fast low angle shot sequence was obtained to localise the biliary tree. Multisection imaging using a T2 weighted half-Fourier acquisition single shot turbo spin echo (HASTE) sequence was used with an effective echo time of 87ms, one excitation, and a 128 x 256 matrix. Fourteen 5mm sections were aquired in a single breath hold. A projection image was performed to obtain a single thick slice covering of the common bile duct in the coronal and oblique-coronal planes. A fat supressed heavily T2 weighted single shot rapid acquisition with relaxation ehnacement (RARE) sequence was used with an effective echo of 1100ms, one excitation, and a 240 x 256 matrix. A 40mm thick section was aquired in a single breath hold of 2s. The test was considered positive if it showed a round, oval, or multifaceted area of signal void within the lumen of the hyperintense bile duct. **Number unable to participate in the index test and reasons given:** None
	(2) CT cholangiography **Test:** 4 slice helical CT scanner with rotation time of 0.5s (Aquilion). Patients were scanned after a fast >4hrs. Each examination consited of 2 phases. First a pre contrast helical CT of the abdomen was carried out with the scanning parameters of 120kVp, 200mAs, 2mm collimation and a table speed of 12mm per rotation. Images were reconstructed with 10mm thickness and 10mm interval. The the patient received an intravenous infusion of cholangiographic contrast agent

(iotroxic acid) for a second scan which was performed with the scanning parameters of 120kVp, 150mAs, 0.5 collimation and a table speed of 1.75mm per rotation. Images were reconstructed with 0.5mm thickness and 0.3mm interval. Multiplanar reconstruction and maximum intensity projection images were created using an independet console (Advantage workstation).

The test was considered positive for CBDS if it showed an intraductal filling defect or abrupt crab claw like termination at the end of the lower bile duct. Unenhanced CTs were reviewed fior a hyperattenuaing ring surrounded by hypoattenuating bile or a structure with soft tissue attenuation within the bile duct.

Number unable to participate in the index test and reasons given: None

(3) EUS

Test: EUS was performed with a 360 degree secotr scanning echoendoscope, Olympus JF-UM200 or GF-UMP230. The endoscopists who performed EUS had an experience in pancreatobiliary diseases for at least years with more than 100 cases per year. Patients were examined in the left lateral position after an overnight fast. Conscious seation was achieved with diazepam. Scopolamin butylbromide or glucagon were given to supresss bowel movement. A water filled balloon was used to establish acoustic coupling.

The test was considered positive for CBDS if a hyperechoic structure associated with acousitc shadowing was found inside the extrahepatic bile duct.

Number unable to participate in the index test and reasons given: -

Results

MRCP

		Reference test		
		+	**-**	**Total**
Index test	**+**	21 (TP)	1 (FP)	22
	-	3 (FN)	3 (TN)	6
	Total	24	4	28

Sensitivity: 0.875 (95%CI: 0.722, 1.000); Specificity: 0.750 (95%CI: 0.201, 1.000)
LR+: 3.500 (95%CI: 0.637, 19.238); LR−: 0.167 (95%CI: 0.050, 0.553)

CT cholangiography

		Reference test		
		+	**-**	**Total**
Index test	**+**	21 (TP)	1 (FP)	22
	-	3 (FN)	3 (TN)	6
	Total	24	4	28

Sensitivity: 0.875 (95%CI: 0.722, 1.000); Specificity: 0.750 (95%CI: 0.201, 1.000)
LR+: 3.500 (95%CI: 0.637, 19.238); LR−: 0.167 (95%CI: 0.050, 0.553)

EUS

		Reference test		
		+	**-**	**Total**
Index test	**+**	24 (TP)	2 (FP)	26
	-	0 (FN)	2 (TN)	2
	Total	24	4	28

Sensitivity: 1.000 (95%CI: 0.979, 1.000); Specificity: 0.500 (95%CI: 0.000, 1.000)
LR+: 1.960 (95%CI: 0.814, 4.717); LR−: 0.040 (95%CI: 0.002, 0.713)

Karki et al. (2013)

Patient characteristics	**Population:** Patients presenting to radioiagnosis department between March 2011 and August 2012 with suspected obstructive jaundice (symptomatic and asymptomatic) deranged liver function tests (raised total, direct bilirubin and alkaline phosphatase). Immediate post ERCP cases were excluded. **Number of patients included:** 88 **Number of patients excluded:** Not stated **Mean age:** 50.27 (range= 5 to 82) **Males/females:** 29 males, 59 females **Country:** India **Other comments:**
Reference standard	**ERCP** The final diagnosis was made by ERCP and /or CT, surgery and confirmed histopathologically
Index test(s)	**Ultrasound** Sonographic evaluation was performed in Siemens acusion x-150 and x-300 using 3.5MHz convex transducer in supine and lateral decubitus position in all patients preferably after an overnight fast.
Results	No frequency data provided **Obstructive jaundice** Sensitivity= 94.8% Specificity= 100% **Common bile duct stones** Sensitivity= 100% Specificity= 89% **Pancreatitis** Sensitivity= 94% Specificity= 66.67% **Biliary tract dialatation** Sensitivity= 94.8% Specificity= 100%

Park et al. (1998)

Patient characteristics	**Population:** Patients with symptoms of acute choelcystitis (sudden onset of right upper quadrant tenderness, low grade fever and leukocytosis) who were referred for ultrasound. **Number of patients included:** 43 **Number of patients excluded:** 8 who did not undergo surgery (presumably because cholecystitis was no longer suspected) **Mean age:** 59 years **Males/females:** 20 males, 15 females **Country:** South Korea **Other comments:** This study also reports diagnostic accuracy for US and MR at evaluating cystic duct obstruction, with surgery as the reference standard. As surgery is not an acceptable reference standard for this part of the biliary tree the cystic duct outcomes have not been extracted.
Reference standard	**Reference standard:** Surgery **Details:** US and MR findings were compared with surgical findings with respect to gallbladder wall thickening and the presence and location of calculi. **Number unable to participate in the reference test :** none
Index test(s)	**(1) Ultrasound for diagnosing acute cholecystitis** **Test:** Real time US was performed a 128XP/10 unit (Acuson) and a 3.5 MHz

transducer. A concerted effort was made to visualise the gallbladder neck and as musch of the cystic duct as possible. The gallbladder neck was imaged where it came into contact with the main segment of the right portal vein or at the main portal vein near the origin of the left portal vein. An attempt was made to determine whether a calculus seen in this area moved with a change in patient position. Additional images slightly medial to the gallbaldder neck were also obtained to discern whether an acoustic shadow emanated from the region of the cystic duct.

All US findings were interpreted by one of 3 radiologists. Image analysis focused on identifying calculi and gallbaldder wall thickening. The criterion used to detect gallbladder wall thickening at US was a wall thickness of more than 4mm

Number unable to participate in the index test and reasons given: -

(2) MRCP for diagnosing acute cholecystitis

Test: MR imaging was performed with a 1.5-T superconducting unit (Magnetom Vision) and phased array body coil. Performed with a half-Fourier rapid acquisition with relaxation ehancement sequence with breath holds. Sequential multisection acquisition (3-5mm thickness, imaging time 18 seconds) was used followed by maximum intensity projection reconstruction. Oblique coronal images (from -20 to +20 degres) were usually obtained, but saggital or axial images were obtained if the cystic duct was not visualised. Imagin parameters were echo train length 128, effective echo time 95msec, field of view 32-35 cm, matrix 240 x 256. Fat saturation was routinely used.

MR cholangiographic source images were analysed individually at te independent MR imaging console after three dimension reconstruction with a maximum intensity projection algorithm. Images were reviewed by two radiologists who were blinded to the patients clincial information and US findings. Image analysis focused on identifying calculi and wall thickening. Calculi were considered present when a signal void was identified within the gallbladder on images obtained in at least two different projections. Wall thickening was identified as an area of intermediate to high signal intensity surrounding the gallbaldder lumen.

Number unable to participate in the index test and reasons given: None

Results

Ultrasound for diagnosing acute cholecystitis- Gallbladder wall thickening

		Reference test		
		+	**-**	**Total**
Index test	**+**	28 (TP)	1 (FP)	29
	-	1 (FN)	5 (TN)	6
	Total	29	6	35

Sensitivity: 0.966 (95%CI: 0.882, 1.000); Specificity: 0.833 (95%CI: 0.452, 1.000)
LR+: 5.793 (95%CI: 0.967, 34.715); LR−: 0.041 (95%CI: 0.006, 0.293)

MRCP for diagnosing acute cholecystits - Gallbladder wall thickening

		Reference test		
		+	**-**	**Total**
Index test	**+**	20 (TP)	1 (FP)	21
	-	9 (FN)	5 (TN)	14
	Total	29	6	35

Sensitivity: 0.690 (95%CI: 0.504, 0.875); Specificity: 0.833 (95%CI: 0.452, 1.000)
LR+: 4.138 (95%CI: 0.680, 25.178); LR−: 0.372 (95%CI: 0.194, 0.713)

Polkowski et al. (1999)

Patient characteristics

Population: Consecutive inpatients referred for ERCP because of suspected CBDS based on clinical symptoms (biliary colic, jaundice, cholangitis, acute pancreatitis) and/or biochemical abnormalities (raised serum aminotransferases, alkaline phosphatase, gamma glutamyl transpeptidase) and/or pathological ultrasound findings (bile duct dilation, bile duct stones).

	Included participants met the following criteria (1) the bilirubin level was less than 334mmol/l (20 mg/l), (2) there was no need for immedate endoscopic treatment, (3) no renal function impairment, (4) no history of iodine allergy. **Number of patients included:** 79 **Number of patients excluded:** 27 due to elevated bilirubin levels (14), known iodine allergy (2), under 18 years of age (1), need for immediate endoscopic treatment (1), lack of patient consent (5), administrative reasons. **Mean age:** Median age = 57 years (range= 34 to 83) **Males/females:** 8 males, 44 females **Country:** Poland **Other comments:** This study also presents diagnostic test accuracy data for EUS which was used as the index test compared to ERCP used as the reference standard. This has not been extracted as the GDG agreed that EUS and ERCP are both reference standards.
Reference standard	**Reference standard:** ERCP **Details:** ERCP was performed in the standard manner using an Olympus TJF 30 or JF 30 duodenoscope. If the endoscopist failed to cannulate the common bile duct the procedure was repeated the following day. Endoscopic sphincterotomy was attempted when ERCP disclosed stones or the common bile duct was dilated. In patients with a clear cholangiogram and undilated common bile duct, sphincterotomy was not attempted. **Number unable to participate in the reference test :** 2 due to failure to cannulate ERCP failed to detect stones in 3 patients- these were discovered only after sphincterotomy was performed
Index test(s)	**(1) Helical CT Cholangiography** **Test:** Scanning was performed on Elscint CT twin flash helical CT with two rows of detectors. Patients were examined in the supine position. No fasting was required. Each examination consisted of two phases. The first pre cholangiography plain helical CT was carried out first, without any contrast. The scanning parameters were 120kVp, 166mAs, pitch 1.5, collimation 8mm. Images were reconstructed every 8mm. After the first phase was completed, the patient received an intravenous infusion of meglumine salt of adipiodone. No pretreatment with antihistamines or corticosteroids was administered. The patients were also given about 500ml water orally to distend the stomach and duodenum. The second phase was performed 19 to 140 minutes after the end of contrast infusion. The scanning parameters were 120 kVp, 166mAs, pitch 1.5, collimation 5mm. Inages were reconstructed every 2mm. Multiplanar and maximum intensity projection images were created using an independent console (Omnipro). All scans were interpeted by a radiologist with 5 years experience in abdominal CT and familiar with the conventional intravenous cholangiography technique. Unenhanced HCT was considered positive if a calcific area was identified within the extrahepatic bileduct; other criteria for CT diagnosis of CBDS were not used. The HCT cholangiography was considered positive if intraductal filling defects were present. Indirect signs such as abrupt termination if the common bile duct or its dilation were not considered indicative of the presnece of stones. At the end of the study an additional retrospective review of unenhanced CT scans was conducted. All scans were reviewed carefully for the following diagnostic criteria: a) hypoattenuating ring surrounded by hypoattenuating bile or b) a structure with soft tissue attenuation present within the bile duct. **Number unable to participate in the index test and reasons given:** None **(2) EUS** **Test:** EUS was performed with a 360 degree sector scanning echoendoscope (Olympus GF-UM20). All examinations were performed by the same endosonographer, whose expertise was based on about 700 previous EUS procedures. Patients were examined on the left lateral position after an overnight fast. Conscious sedation was achived with intravenous midazolam. A water filled balloon was used to establish acoustic coupling. No antispasmodic agents were

used. The transducer was introduced into the second portion of the duodenum and slowly pulled back. This procedure was repeated several times. Pancreatiic head, periampullary region and extrahepatic bile duct were visualised from the descending duodenum or duodenal bulb, and searched for pathology such as stones or tumours.

EUS was considered postive if it showed single or multiple hyperechoic structures located within the extrahepatic bile duct and associated with acousitic shadowing

Number unable to participate in the index test and reasons given: -

Results

Helical CT Cholangiography

		Reference test		
		+	**-**	**Total**
Index test	**+**	29 (TP)	2 (FP)	31
	-	3 (FN)	14 (TN)	17
	Total	32	16	48

Sensitivity: 0.906 (95%CI: 0.790, 1.000); Specificity: 0.875 (95%CI: 0.682, 1.000)

LR+: 7.250 (95%CI: 1.974, 26.634); LR−: 0.107 (95%CI: 0.036, 0.320)

EUS

		Reference test		
		+	**-**	**Total**
Index test	**+**	31 (TP)	0 (FP)	31
	-	3 (FN)	16 (TN)	19
	Total	34	16	50

Sensitivity: 0.912 (95%CI: 0.802, 1.000); Specificity: 1.000 (95%CI: 0.969, 1.000)

LR+: 30.600 (95%CI: 1.990, 470.584); LR−: 0.103 (95%CI: 0.038, 0.279)

Regan et al. (1996)

Patient characteristics	**Population:** Over a 20 month period, patients with suspected CBDS due to clinical suspicion or sonographic evidence of CBDS **Number of patients included:** 26 **Number of patients excluded:** 3 due to unsucessful ERCP (2) and intolerance of MR due to claustrophobia (1) **Mean age:** 68 years (range= 42 to 89) **Males/females:** 10 males, 13 females **Country:** USA **Other comments:** -
Reference standard	**Reference standard:** ERCP **Details:** ERCP was performed by an experienced gastroenterologist using a side viewing endoscope (Olympus). Fluoroscopy was performed by a radiology technician and images were interpeted by two observers using standard diagnostic criteria. **Number unable to participate in the reference test :** 2 due to large periampullary diverticulae
Index test(s)	**(1) MR (HASTE)** **Test:** Imaging was done using a 1.5T Magnetom Vision Imager using the standard circular polarised body coil. HASTE sequence was applied twice in the axial, coronal, and oblique saggital imaging planes using a gap and fill imaging technique. 6 scans with 12 images for each scan yeilded 24 images in each of the imaging planes. The oblique saggital imaging plane was applied parallel to the common bile duct as shown by the initial coronal images. A acquisition time of 13 sec allowed scanning during a single breath hold. To avoid misregistration artefacts patients were instructed to hold their breath in the same fashion for each of the 6 scans. The following parameters were used: 8.2/66 (TR/effective TE), echo train length 128, 1 exclitation, matrix sixe 128 x 256, field view 360 x 360mm, 4mm slice thickness, fat supression. Three dimensional cholangiograms were obtained by post processing on remote consoles using MIP from original image volume edited to include the biliary tree. Contrat agents and antiperistalic drugs were not used. CBDS were diagnosed when round or multifaceted signal voids were seen in the lumen in at least two imaging planes **Number unable to participate in the index test and reasons given:** 1 due to claustrophobia
	(2) US **Test:** US was done in a conventional fashion by an experienced sonographer, a physician with an interest in sonography, or both using a XP10 (Acuson) or Ultramark 9 (Advanced Technology Laboratories) machine using 3.5 or 5.0MHz transducers. **Number unable to participate in the index test and reasons given:** None
Results	**MR (HASTE)**

		Reference test		
		+	**-**	**Total**
Index test	**+**	14 (TP)	1 (FP)	15
	-	1 (FN)	7 (TN)	8
	Total	15	8	23

Sensitivity: 0.933 (95%CI: 0.774, 1.000); Specificity: 0.875 (95%CI: 0.583, 1.000)
LR+: 7.467 (95%CI: 1.188, 46.937); LR−: 0.076 (95%CI: 0.011, 0.515)

US

	Reference test		
	+	**-**	**Total**

	Index test	**+**	9 (TP)	0 (FP)	9
		-	6 (FN)	8 (TN)	14
		Total	15	8	23
	Sensitivity: 0.600 (95%CI: 0.319, 0.881); Specificity: 1.000 (95%CI: 0.938, 1.000) LR+: 10.688 (95%CI: 0.701, 162.896); LR−: 0.430 (95%CI: 0.233, 0.794)				
	Paper reports that specificity was 87.5%, but calculations using the data provided by the paper indicates specificity is 89%				

Rickes et al. (2006)

Patient characteristics

Population: Patients with clincal and/or biochemical signs of CBDS based on a combination of epigastric or right upper quadrant pain with fever or jaundice; one or two of the previous signs together with an elevated serum alkaline phosphatase level or an increase in serum gamma glytamyl transpeptidase or transaminase level above the upper limit of normal; acute pancreatitis; unexplained cholestasis. Patients were excluded if long term daily alcohol intake exceeded 80g, if they were taking hepatoxi drugs, if serum hepatitis B or C antibodies were present, or if they refused to undergo US and/or ERCP

Number of patients included: 126

Number of patients excluded: 2 were excluded for refusing ERCP

Mean age: 63.2 years (range= 21 to 91)

Males/females: 38 male, 86 female

Country: Germany

Other comments: None

Reference standard

Reference standard: ERCP

Details: ERC procedures were performed within 24hours of US by experienced gastrointestinal endoscopists using a standard technique with an Olympus duodenoscope.

Interpetation was done by the endoscopist performing the procedure. An instrumetal exploration of the common bile duct using Dormia baskets and/or retrieval balloon passage through the bile duct was performed in all cases after sphincterotomy. The presence of CBDS was confirmed on their removal or if they were actually seen passing through the sectioned sphincter into the duodenal lumen.

Number unable to participate in the reference test : 2 refused the test

Index test(s)

(1) Ultrasound

Test: Patients were randomised to an experienced (more than 4 years experience and over 10,000 own investigations) or inexperienced (fewer than 4 years experience and less than 2000 own investigations).

US was done using a dynamic 2-5MHz sector scanner (Seimans Elegra). The diagnostic criteria for CBDS was a hyperechoic structure within the common bile duct sometimes associated with an acoustic shadow. The CBD was considered enlarged if the diameter was more than 7mm (or 10mm for patients who had undergone choleystectomy).

Number unable to participate in the index test and reasons given: None

Results

Ultrasound - Experienced investigator

		Reference test		
		+	**-**	**Total**
Index test	**+**	22 (TP)	1 (FP)	23
	-	5 (FN)	7 (TN)	12
	Total	27	8	35

Sensitivity: 0.815 (95%CI: 0.650, 0.980); Specificity: 0.875 (95%CI: 0.583, 1.000)
LR+: 6.519 (95%CI: 1.033, 41.134); LR−: 0.212 (95%CI: 0.092, 0.487)

Ultrasound - Inexperienced investigator

		Reference test		
		+	**-**	**Total**
Index test	**+**	25 (TP)	3 (FP)	28
	-	29 (FN)	32 (TN)	61
	Total	54	35	89

Sensitivity: 0.463 (95%CI: 0.321, 0.605); Specificity: 0.914 (95%CI: 0.807, 1.000)
LR+: 5.401 (95%CI: 1.763, 16.546); LR−: 0.587 (95%CI: 0.449, 0.768)

Shiozawa (2005)

Patient characteristics	**Population:** Patients undergoing laparoscopic cholecystectomy for cholecystitis. ERCP was performed preoperatively regardless of clinical and laboratory data. **Number of patients included:** 513 **Number of patients excluded:** 3 no reasons provided **Mean age:** 57.1 years (range= 15 to 90) **Males/females:** 224 male, 286 female **Country:** Japan **Other comments:**
Reference standard	**Reference standard: ERCP** **Details:** ERCP performed with an Olympus videoendoscope (JF230). Patients with no cholangiographic evidence of CBDS went direct to laparascopic cholecystectomy. Patients with evidence of CBDS on cholangiogram had endoscopic papillo-sphincterotomy performed with a papillotome (KD-20Q-I) or a balloon catheter (B7-2LA). When it was judged to be difficult to remove CBDS by papillosphincterotomy because they were large (greater than or equal to 2cm) or because of multiple stones, cholecyst-chole-docholithotomy was performed without laparascopic cholecystectomy. **Number unable to participate in the reference test:** ERCP success rate was 99.4%
Prognostic factors	This study investigated the following factors for predicting CBDS: age, gender, abdominal pain, fever elevation, jaundice, pancreatitis, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin (TBIL), gamma glutamyl transpeptidase (GGT), alkaline phosphatase (ALP), amylase (AMY), and ultrasound findings. The following factors were found to be significant in univariate analyses and were analysed using multivariate logistic regression: Jaundice, pancreatitis, ALT, TBIL, ALP, AMY, CBD dilation on US. ALP (<298U/L), TBIL (<1.2mg/dl), AMY (<180U/L), CBD dilation on US (>8mm) were found to be significant in the multivariate model, and diagnostic test accuracy was performed using these variables.
Results	

		ERCP	
		+	-
Any one of the 4 significant factors (ALP, Bil, AMY, CBD dilation >8mm)	+	81 (TP)	22 (FP)
	-	2 (FN)	405 (TN)

Sensitivity: 0.976 (95%CI= 0.937, 1.00) Specificity: 0.948 (95%CI= 0.926, 0.971)
LR+: 18.94 (95%CI= 12.59, 28.49); LR−: 0.025 (0.006, 0.100)

Soto et al. (2000)

Patient characteristics	**Population:** Patients referred for ERCP because of suspected CBDS.The following patients were excluded: under the age of 18, creatinine level greater than 1.3mg/dL, bilirubin level greater than 5md/dL, known hyperuricemia, contraindicated for MR because of aneurysm clips, cardiac pacemakers, and incompatible implants **Number of patients included:** 68 **Number of patients excluded:** 17- because they did not meet the incusion criteria (12), Claustrophobia (2), ERCP not attempted (1), ERCP not completed (2) **Mean age:** 53 years (range= 18 to 84) **Males/females:** 19 males, 32 females **Country:** Colombia **Other comments:** -
Reference standard	**Reference standard:** ERCP **Details:** Performed after the test under comparison were completed. Performed by one of 3 gastrointestinal endoscopists using a standard technique Images were interpreted without the knowledge of CT or CT cholangiography findings **Number unable to participate in the reference test :** 3, 1 not attepmted (no reason given), 2 not completed (no reasons given)
Index test(s)	**(1) CT (unenhanced)** **Test:** Performed by a helical CT scanner (ProSpeed). Studies were obtained in the supine position after fasting for at least 4 hours. To define the area of interes to be included in the helical acquisitions, low dose axial images of the liver and pancreas were initially obtained. Scanning parameters for these initial images were non helical acquisition, 10mm collimation, 10mm table feed, 120kVp, and 160mAs. Scans were obtained in a caudocranial direction starting and the third portion of the duodenum. Parametes used for helical CT aquistion were 30 to 36 sec scan time, one tube rotation per second at a current of 250mAs and 120kVp, 3mm collimation, and 5mm/sec table speed. The field of view for scanning ranged from 280 to 380 mm depending on patient size. Patients unable to hold their breath were instructed to breathe quietly. The volumetric data were reconstructed at 1mm intervals using 180 degree linear interpolation algorithm and high density kernel. No additional oral or IV contrast material was administered. Test was considered positive for stones if intraductal foci with an attenuation coefficient that differed from that of the surrounding bile was observed. No clinical information or results of other tests were provided to the interpreting radiologists **Number unable to participate in the index test and reasons given:** None
	(2) CT cholangiography (oral enhanced) **Test:** Helical CT scanner (ProSpeed). The total dose of iopodic acid administered was 6g given in 2 doses (1st dose 2hrs after dinner, 2nd dose 2hrs later). Cholangiograms were perfomred between 7am and 9am the following morning. People with prior cholecystectomy and were examined in a fasting state. People with their gall baldder in situ were given a fatty meal 20 to 30 mins prior to examination to induce gallbladder contraction. No other contrast agent was used. Test was considered positive for stones if intraductal foci with an attenuation coefficient that differed from that of the surrounding bile was observed. No clinical information or results of other tests were provided to the interpreting radiologists **Number unable to participate in the index test and reasons given:** None
	(3) MR cholangiography **Test:** Performed on a 1.5-T system (ACS NT) with a body coil. Performed using 3 different pulse sequences: breath hold, single shot half Fourier rapid acquisition with relaxation enhancement (in single and multislice modes), and non breath hold three dimensional fast spin echo with respiratory triggering. Scanning parameters for single slice RARE were infinite/300 (TR/Teeff), 30mm slice thickness, one acquisition, 128 x 256 matrix, 128 echo train length, 9.9msec echo spacing, and

acquisition time of 2.5 sec per slice. For multislice RARE sequence, parameters were infinite/290 (TR/Teeff), 5mm slice thickness, 10 slices, one acquisition, 128 x 256 matirx, 128 echo train length, 9msec echo spacing and 20 sec acquisition time. For the three dimenaional fast spin echo sequence, the following parameters were used: 2000-2300/240 (TR range/TEeff), 2mm partition thickness (40 portions, 8 slabs), two acquisitions, 128 x 256 matrix 39-43 echo train length, 12msec echo spacing, and nominal acquisition time of 5min 40 sec to 6 min 20 sec. A chemically selective fat saturation pre pulse was used for the three sequences. A 65% partial K-space filling factor was applied for both half-Fourier RARE sequences. The 3D fast spin echo an multislice half-Fourier RARE sequences were aquired in a right anterior oblique-coronal plane. For the single half-Fourier sequence, four different projections, each with a different orientation were obtained. No oral or anti peristaltic agent was administered.

All three sequences were acuired in 17 patients, Only breath hold sequences aquired in 31 patients, and only non breath hold sequence in 3 patients. A chemically selective fat saturation prepulse was used for the tree sequences.

Number unable to participate in the index test and reasons given: -

Results

CT (unenhanced)

		Reference test		
		+	**-**	**Total**
Index test	**+**	17 (TP)	4 (FP)	21
	-	9 (FN)	21 (TN)	30
	Total	26	25	51

Sensitivity: 0.654 (95%CI: 0.452, 0.856); Specificity: 0.840 (95%CI: 0.676, 1.000)
LR+: 4.087 (95%CI: 1.595, 10.469); LR−: 0.412 (95%CI: 0.236, 0.718)

CT cholangiography (oral enhanced)

		Reference test		
		+	**-**	**Total**
Index test	**+**	24 (TP)	2 (FP)	26
	-	2 (FN)	23 (TN)	25
	Total	26	25	51

Sensitivity: 0.923 (95%CI: 0.801, 1.000); Specificity: 0.920 (95%CI: 0.794, 1.000)
LR+: 11.538 (95%CI: 3.040, 43.799); LR−: 0.084 (95%CI: 0.022, 0.318)

MR cholangiography

		Reference test		
		+	**-**	**Total**
Index test	**+**	25 (TP)	0 (FP)	25
	-	1 (FN)	25 (TN)	26
	Total	26	25	51

Sensitivity: 0.962 (95%CI: 0.868, 1.000); Specificity: 1.000 (95%CI: 0.980, 1.000)
LR+: 49.111 (95%CI: 3.150, 765.581); LR−: 0.057 (95%CI: 0.012, 0.269)

Soto et al. (1999)

Patient characteristics	**Population:** All patients referred for ERCP because of suspected CBDS. The following inclusion criteria had to be met: age 18 years or over, bilirubin level of 5.0mg/dL or less, a creatinine level of 1.3mg/dL or less, no previous allergic reaction to iodinated contrast media, no known hyperuricemia. **Number of patients included:** 31 **Number of patients excluded:** Not stated **Mean age:** 43 years (range= 19 to 86) **Males/females:** 11 males, 20 females **Country:** Colombia **Other comments:** -
Reference standard	**Reference standard:** ERCP **Details:** Technical details not stated. ERCP was interpretted by a gastroenterologist performing the procedure and a radiologist who was not involved. **Number unable to participate in the reference test :** 2 due to cannulation failure
Index test(s)	**(1) CT cholangiography (oral contrast enhanced)** **Test:** Tests were condicted within 48hrs of the scheduled ERCP. Iopanoic acid was administered orally the night befoe the CT examination. Patients were instructed to eat their usual meal no later than 6pm, and to take 3g at 8pm and 3g at 11 pm. CT was done between 7 and 8am the next day. 20-30 mins before the CT examination patients with their gall baldders in situ were given a fatty meal to incude gallbladder contraction. No other contrast material was given. A ProSpeed scanner or a PQ 5000 scanner was used to examine patients with an identical CT technique used for both. To define the area of interest to be included in the helical acquisition low dose axial images of the liver and pancreas were obtained. The scan parameters for these initial images were non helical acquisition, 10mm collimation, 10mm table feed, 120kVp, and 160mAs. From this initial set of images the duodenum was identified for each patient and was set as the caudal extent of the helical acquisition. For the CT cholangiography examination data were aquired in a caudocephallic direction during a single breath hold. Scan parameters were a scan time of 30 to 36 sec, one tube rotation per sec at a current of 250mAs and 120kV, a collimation of 3mm and a table speed of 5mm sec with pitch factor 1.67. A retrospective reconstruction of the data set at 1mm intervals was done using a 190 degree linear interpolation algorithm and a high density kernal. For post processing, the complete set of reconstructed source images was then transferred to an independent workstation (General Electric Advantage Windows for images obtained using the General Electric system, or the Voxel Q workstation for images obtained using the Picker International system. 2 radiologists interpreted each set of images, and the single finding that each radiologist was asked to record was the presence or absence of CBDS. Biliary opacification was quantified by measuring the the density of opacified bile in the intrapancreatic portion of the CBD using circular or oval regions of interest. All these measurements were made from the axial source images by a radiologist who was not involved in image interpretation. The same radiologist determined the caliber of the CBD using electronic calipers and software provided with the workstations by the manufacturers. CBD diameter was defined as the maximum short axis dimension of the extrahepatic bile duct, to avoid overestimation of the caliber of the duct from scanning in the oblique plane. These measurements were also made at the workstations, and 6mm was used as the upper limit of normal for patients with a gallbladder, and 8mm for patients with a history of cholecystectomy. **Number unable to participate in the index test and reasons given:** None
Results	**CT cholangiography (oral contrast enhanced) - Radiologist 1**

	Reference test		
	+	**-**	**Total**

Index test	**+**	13 (TP)	0 (FP)	13
	-	1 (FN)	15 (TN)	16
	Total	14	15	29

Sensitivity: 0.929 (95%CI: 0.758, 1.000); Specificity: 1.000 (95%CI: 0.967, 1.000)
LR+: 28.800 (95%CI: 1.872, 443.075); LR−: 0.103 (95%CI: 0.023, 0.472)

CT cholangiography (oral contrast enhanced) - Radiologist 2

		Reference test		
		+	**-**	**Total**
Index test	**+**	12 (TP)	0 (FP)	12
	-	2 (FN)	15 (TN)	17
	Total	14	15	29

Sensitivity: 0.857 (95%CI: 0.638, 1.000); Specificity: 1.000 (95%CI: 0.967, 1.000)
LR+: 26.667 (95%CI: 1.726, 411.966); LR−: 0.172 (95%CI: 0.055, 0.535)

Stiris et al. (2000)

Patient characteristics	**Population:** Patients with clinically and laboratory suspected CBDS **Number of patients included:** 50 **Number of patients excluded:** Not stated **Mean age:** 60 years (range= 19 to 94) **Males/females:** 13 males, 37 females **Country:** Norway **Other comments:** -
Reference standard	**Reference standard:** ERCP **Details:** Performed in the fluoroscopy unit by one of the clinicans experienced in the procedure. The procedure was supervised by one of the radiologists to obtain optimal diagnostic information **Number unable to participate in the reference test :** None
Index test(s)	**(1) MRCP** **Test:** Images were aquired with a superconducting magnet operating at 1.0 T (Magnetom Expert) using a breath hold HASTE sequence with body phased array coil through the liver and pancreas. The TR/TE was 10.92/87ms, respectively with a matrix of 240 x 256, 128 echo train, and a field of view of 280 for small patients and 300 for large patients. This is a 5mm slice thickness multislice technique in which 13 slices in a 19s breath hold are aquired. The slice most suitable for further evaluation was selected. From this slice right and left oblique coronal (10 to 40 degrees) and coronal projections with a HASTE fat surpresse dequence (using same parameters as above with additional fat supression) was selected. The fat supression was added to decrease the signal intensity of periductal fat containing tissues. Maximum intensity projection was then applied for reformatting the slices on a work station. Volume of interest was also applied when necessary to remove overprojected ventricle and intestines. All the source images were used in each patients for the evaluation. The result was written down and put in an envelope which was sealed. **Number unable to participate in the index test and reasons given:** None
Results	**MRCP**

		Reference test		
		+	**-**	**Total**
Index test	**+**	28 (TP)	1 (FP)	29
	-	4 (FN)	17 (TN)	21
	Total	32	18	50

Sensitivity: 0.875 (95%CI: 0.745, 1.000); Specificity: 0.944 (95%CI: 0.811, 1.000)
LR+: 15.750 (95%CI: 2.334, 106.280); LR−: 0.132 (95%CI: 0.053, 0.333)

Sugiyama & Atomi (1997)

Patient characteristics	**Population:** Consecutive patients referred for ERCP because of suspected CBDS. All patients met at least one of the following criteria for ERCP: epigastric or right upper quadrant pain with fever (75 patients), jaundice (81 patients), abnormal liver chemistry (102 patients), dilated common bile duct (>7mm) (83 patients), recent acute pancreatitis (21 patients) **Number of patients included:** 155 **Number of patients excluded:** 17 due to unclear cholangiogram on ERCP **Mean age:** Not stated **Males/females:** Not stated **Country:** Japan **Other comments:** -
Reference standard	**Reference standard:** ERCP **Details:** No details provided **Number unable to participate in the reference test :** None but 3 patients experienced complications (2 mild pancreatitis, 1 acute cholangitis)
Index test(s)	**(1) EUS** **Test:** EUS was performed using an echoendoscope with 7.5MHz rotating transducer (Olympus GF-UM2/EU-M2 or GF-UM3/EU-M3). After the scope was introduced into the descending duodenum the extrahepatic bile duct and gallblader were scanned while the scope was slowly withdrawn. A balloon filled with water was used to provide acoustic coupling. For sedation 5 to 10mg of diazepam was administered intravenously. CBDS were diagnosed when a definite echogenic focus with or without shadowing in the common bile duct was deomnstrated. **Number unable to participate in the index test and reasons given:** None
	(2) Ultrasound **Test:** Ultrasound was performed using a real time scanner with a 3.5-MHz curved array transducer (Toshiba SSA-270A or SAL-77A). The diagnosis of CBDS was the same as EUS **Number unable to participate in the index test and reasons given:** None
	(3) CT **Test:** CT was done with a W200 scanner (Hitachi Medico) or a YG0314 scanner (Yokogawa Medical). The upper part if the abdomen was scanned in 5mm sections at 5mm intervals before and after a rapid bolus injection of 60% iodinated contrast material. CBDS was diagnosed when a round high density mass surrounded by bile within the CBD was visualised. **Number unable to participate in the index test and reasons given:** None
Results	**EUS**

		Reference test		
		+	**-**	**Total**
Index test	**+**	49 (TP)	0 (FP)	49
	-	2 (FN)	91 (TN)	93
	Total	51	91	142

Sensitivity: 0.961 (95%CI: 0.898, 1.000); Specificity: 1.000 (95%CI: 0.995, 1.000)
LR+: 175.154 (95%CI: 11.031, 2781.108); LR−: 0.048 (95%CI: 0.014, 0.162)

Ultrasound

		Reference test		
		+	**-**	**Total**
Index test	**+**	32 (TP)	5 (FP)	37
	-	19 (FN)	86 (TN)	105

	Total	51	91	142

Sensitivity: 0.627 (95%CI: 0.485, 0.770); Specificity: 0.945 (95%CI: 0.893, 0.997)
LR+: 11.420 (95%CI: 4.746, 27.475); LR−: 0.394 (95%CI: 0.275, 0.565)

CT

		Reference test		
		+	**-**	**Total**
Index test	**+**	36 (TP)	3 (FP)	39
	-	15 (FN)	88 (TN)	103
	Total	51	91	142

Sensitivity: 0.706 (95%CI: 0.571, 0.841); Specificity: 0.967 (95%CI: 0.925, 1.000)
LR+: 21.412 (95%CI: 6.939, 66.071); LR−: 0.304 (95%CI: 0.198, 0.466)

Sugiyama et al. (1998)

Patient characteristics	**Population:** Non consecutive patients recruited in an arbitrary manner, without known selection bias, recruited from the pool of all patients referred for ERCP because of suspected CBDS. All patients met at least one of the following criteria: epigastric or right upper quadrant pain with fever, jaundice, abnormal blood liver chemistry, bile duct stones, or a dilated CBD (>7mm) on unltrasound, or recent acute pancreatitis. Patients with ultrasonography clearly demonstrating malignacy and patients with previous sphincterotomy or biliary drainage were also excluded. **Number of patients included:** 101 **Number of patients excluded:** 7 due to unclear ERCP **Mean age:** 61 years (range= 16 to 92) **Males/females:** 45 male, 56 female **Country:** Japan **Other comments:** -
Reference standard	**Reference standard:** ERCP **Details:** Not described The maximum diameters of CBD and CBDS (the largest stone if multiple) were determined using the known diameter of the endoscope as a correction factor for magnification. **Number unable to participate in the reference test :** 4 had unclear images and were excluded
Index test(s)	**(1) MRCP** **Test:** Performed using a 1.5-T superconductive unit (Magnetom Vision) with a body phased array coil. A HASTE sequence was used with an echo train length of 128, an effective echo time of 87ms, one excitation, and a matrix of 128 x 256 (an aquistion time of 1s) or 240 x 256 (2s). In MRC studies with single slice images of 10mm tickness, matrix sizes were randomly selected. In other studies a matrix of 240 x 256 was employed. HASTE is a single shot sequence and has no repitition time. The field of view was 20-35 cm depending on the area of interest or the patients consitiution. Fat saturation was employed to supress the signal from peritoneal tissue. After axial scans had been obtained for localisation of the biliary tree, coronal or paracoronal (10 to 40 degrees left anterior oblique) images were obtained. Two acquisition techniques were used: single slice (thickness 10-20mm, acquisition time 1-2 s) and sequential multislice (9 sections of 5mm thickness and a total acquisition time of 18s). Sequential multislice images were reconstructed using a maximum intensity projection algorithm. The patients were requested to perform a single breath hold for each acquisition. Neither contrast material nor antiperistaltic drugs were administered. For image analysis both the single slice and MIP images were prepared. The source images for the latter were also available. Images were retrospectively reviewed by one of the investigators who was blind to the ERCP findings. Assessment included visualisation of the CBD and evidence of CBD stones. Criteria for diagnosis of calculi were demonstration of circumscribed areas of signal void and definite echogenic foci with or without shadowing, respectively within the CBD lumen. **Number unable to participate in the index test and reasons given:** None **(2) Ultrasound** **Test:** No details provided Image analysis was the same as described for MRCP **Number unable to participate in the index test and reasons given:** None
Results	**MRCP**

		Reference test		
		+	**-**	**Total**
Index test	**+**	31 (TP)	0 (FP)	31
	-	3 (FN)	63 (TN)	66

		Total	34	63	97
	Sensitivity: 0.912 (95%CI: 0.802, 1.000); Specificity: 1.000 (95%CI: 0.992, 1.000) LR+: 115.200 (95%CI: 7.268, 1825.915); LR−: 0.101 (95%CI: 0.037, 0.272)				
	Ultrasound				
			Reference test		
			+	**-**	**Total**
	Index test	**+**	24 (TP)	3 (FP)	27
		-	10 (FN)	60 (TN)	70
		Total	34	63	97
	Sensitivity: 0.706 (95%CI: 0.538, 0.874); Specificity: 0.952 (95%CI: 0.892, 1.000) LR+: 14.824 (95%CI: 4.810, 45.679); LR−: 0.309 (95%CI: 0.183, 0.521)				
	Study also reports diagnostic accuracy data for diagnosing choledocholithiasis by stone diamenter (3-5mm/ 6-10mm/ 11-27mm) and by diameter of bile duct (4-8mm/ 9-14mm/ 15-39mm). This has not been extracted but can be if needed.				

Tseng et al. (2008)

Patient characteristics	**Population:** Consecutive patients undergoing ERCP for clinically suspected choledocholithiasis who had abdominal CT within 5 days before ERCP. **Number of patients included:** 266 **Number of patients excluded:** Not stated **Mean age:** 72.4 years (range= 29 to 95) **Males/females:** 119 males, 44 females **Country:** Taiwan **Other comments:** None
Reference standard	**Reference standard:** ERCP **Details:** Performed by experienced gastorenterologists with an Olympus JF-240 electronic duodeno-videoscope after premedication with local pharyngeal lidocane spray and an i.m. injection of hyoscine-N-butylbromide. If ERCP images showed movable filling defects, endoscopic sphincterotomy or balloon dilation of the papilla was performed for CBDS extraction. **Number unable to participate in the reference test :** None
Index test(s)	**(1) CT** **Test:** Appears that patients were allocated to one of three different types of CT, but unclear how or why (5mm thick sections with coronal reconstruction, 5mm thick sections without coronal reconstruction, 7mm think sections without coronal reconstruction). CT machines were multislice (Philips Brilliance 40), or single slice (HiSpeed series). The criteria for detecting CBD stones were according to previous studies (a rim of increased density along the CBD without a visible surrounding mass, a rim of increased density along the distal CBD margin proposed as calcification in the margin of an impacted stone, irregular unarganised areas of increased density in the CBD lumen. CT images were interpreted by experienced radiologists who were blinded to the study. **Number unable to participate in the index test and reasons given:** None
Results	**CT**

		Reference test		
		+	**-**	**Total**
Index test	**+**	126 (TP)	28 (FP)	154
	-	37 (FN)	75 (TN)	112

		Total	163	103	266
	Sensitivity: 0.773 (95%CI: 0.706, 0.840); Specificity: 0.728 (95%CI: 0.637, 0.819) LR+: 2.844 (95%CI: 2.051, 3.943); LR−: 0.312 (95%CI: 0.229, 0.424)				

G.3 Included studies question 3

Table 1: Attili (1995)

Patient characteristics	**Population:** 161 civil servants screened for gallstone disease, of which 118 were identified as having asymptomatic gallstones. This diagnosis was made based on a positive ultrasound finding, which was confirmed by oral cystography in some people. Asymptomatic was defined as an absence of biliary colic for the last 5 years. Patients were classified as becoming symptomatic if they experienced an episode of biliary colic during follow up. Information was gained through regular follow up and from family doctors and hospital records **Mean age:** 27 to 74 years **Males/females:** 95 male, 66 women **Country:** Italy **Other comments:** Males and females were recruited in separate recruitment rounds. Unclear why this approach was taken.
Reference standard	Ultrasound
Prognostic factor(s)	The following factors were considered as possible predictors of biliary colic, complications, cholecystectomy, death: Age, sex, body mass index, awareness of having gallstones before diagnosis, gallbladder opacifacation, number of stones, diameter of stones, radiopacity of stones, occurrence of biliary colic.
Length of follow up	10 years, or until they experienced biliary colic, complications, cholecystectomy, or death. Data were collected every 2 years.
Results	<u>Biliary colic</u> None of the variables were found to be associated (either at univariate or multivariate analysis) with an increased risk of developing biliary colic. <u>Complications</u> The low number of events meant that analysis was not possible <u>Cholecystectomy</u> None of the variables tested as possible predictors of cholecystectomy was significantly associated with an increased risk of intervention (*no data provided*), with the exception of the occurrence of biliary colic during follow up (Z= 2.998, p=0.04). The significance of this association was confirmed in a multivariate analysis including age, sex, body mass index, awareness and diabetes. <u>Death</u> *No associations between potential predictive factors and death were reported.*

G.4 Included studies question 4

4a- Asymptomatic gallstones

No evidence meeting the inclusion and exclusion criteria was found.

4b- Symptomatic gallbladder stones

4b.1 Laparoscopic cholecystectomy compared to laparoscopic cholecystectomy with intraoperative cholangiography

Amott, D. et al (2005)

Population	**Category:** Symptomatic gallbladder stones **Number randomised:** 315 **Inclusion criteria:** Patients undergoing laparoscopic cholecystectomy between February 1995 and November 2002. LFTs were regarded as abnormal if one or more of the bilirubin, aspartate aminotransferase or alkaline phosphatase were elevated above the normal range for the research centre laboratory. **Exclusion criteria:** Patients with a preoperative diagnosis of common bile duct stones and people who had undergone preoperative ERCP for suspected or proven CBDS. **Age:** Not stated **Gender:** Not stated **Country:** Australia
Procedure	Randomisation was done by birth month. People with even birth months (Feb, Apr, Jun etc.) were allocated to routine IOC. People with odd birth months (Jan, March, May etc) underwent selective IOC. Randomisation failed in 2 of the patients allocated to routine IOC (did not undergo routine IOC but were analysed as part of this group) Randomisation failed in 8 of the patients allocated to selective IOC (did not undergo selective IOC but were analysed as part of this group)
Arms	**(1) laparoscopic cholecystectomy + routine intra operative cholangiography** N:152 Description: The operation was performed in a standard manner. IOC was performed with Meglumine iotalamate diluted to half strength with normal saline using a 1.5mm soft catheter. This was introduced into the abdomen via a cannula passed directly through the abdominal wall. All patients were scheduled to undergo IOC. 4 patients were lost to follow up from this group (N=148) 94 patients from this group underwent successful IOC **(2) laparoscopic cholecystectomy + selective intra operative cholangiography** N: 163 Description: As above. Only patients with abnormal LFT results and CBD diameter >5mm were scheduled to undergo IOC 8 patients were lost to follow up from this group (N= 155) 45 patients from this group had indications for IOC and 34 patients underwent successful IOC
Results	• **Outcome** / **LC+ routine IOC (n=148)** / **LC+ selective IOC (n=155)** • Bile leak / - / -

	• Bile injury	1/148	1/155	
	• Length of stay	-	-	
	• Missed common bile duct stones	3/148 a	5/155 b	
	• Conversion to open	6/148	Unclear c	

a These patients did not have successful IOC.
b Only one of the 5 patients with postoperative CBDS had undergone IOC
c Study states that five patients had CBDS that were cleared by laparoscopic flushing of the CBD or open duct exploration

Khan,O.A. et al. (2011)

Population	**Category:** Symptomatic gallbladder stones **Number randomised:** 190 **Inclusion criteria:** patients referred to the upper GI surgical outpatient clinic for consideration for elective laparascopic cholecystectomy. Patients presented with a history of biliary colic or cholecystitis and a low predictive risk of CBDS. **Exclusion criteria:** Under the age of 18 years, suspected of CBDS (abnormal LFT results, history of jaundice, pancreatitis, previous ERCP, CBDS on ultrasound, dilated CBD >7mm on ultrasound), history of allergic reaction to contrast material, previous major upper abdominal surgery ASA grade III or more, acalculous cholecystitis, patients with gallbladder polyps. **Age:** Mean= 59 (standard error mean= 2) Surgery + Intraoperative cholangiography Mean= 53 (standard error mean= 2) Surgery alone **Gender:** 15 males, 76 females Surgery + Intraoperative cholangiography 24 males, 75 females surgery alone **Country:** UK
Procedure	Randomisation took place after induction of anaesthesia. Allocation was performed by opening one of 200 sealed and randomly shuffled envelopes, each containing a number between 1 and 200. Even numbers were allocated to the surgery + intraoperative cholangiography group and odd numbers the surgery along group
Arms	**(1) laparoscopic cholecystectomy** N: 99 Description: LC was performed using 4 ports under the supervision of two consultant surgeons utilizing uniform surgical techniques. On table cholangiogram could be perfomed at the discretion of the surgeon in technically demanding cases in order to clarify the biliary anatomy. 9 patients in this group required IOC (and were analysed in the surgery alone arm) **(2) laparoscopic cholecystectomy + Intra operative cholangiography** N: 91 Description: LC was performed using 4 ports under the supervision of two consultant surgeons utilizing uniform surgical techniques. Cholangiography was achieved by performing a ductotom in the cystic duct, extruding any stones within the cystic duct followed by connulation of the duct with a 6Fr umbilical feeding catheter. This was introduced through the abdominal wall via a needle through a separate skin puncture wound and advanced through the cystic duct where it was secured with one titanium clip. Omnipaque solution was then injected into the biliary system and the biliary anatomy was visualised using a mobile C-arm unit and an image intensifier. The images were reviewed by the operating surgeon at the time of surgery. Where any filling defect of the CBD was noted, the patient underwent laparascopic transcystic CBD exploration using a flexible choledochoscope and stone removal with a wire basket. All patients successfully underwent cannulation of the cystic duct. Biliary tree anatomy

	was visulaised in 90 patients
Results	<table><tr><th>Outcome</th><th>LC (n=99)</th><th>LC+IOC (n=91)</th></tr><tr><td>Bile leak</td><td>-</td><td>-</td></tr><tr><td>Bile injury</td><td>1/99</td><td>0/91</td></tr><tr><td>Length of stay</td><td>-</td><td>-</td></tr><tr><td>Missed common bile duct stones</td><td>0/99 a</td><td>0/91</td></tr><tr><td>Conversion to open</td><td>1/99</td><td>0/91</td></tr></table> a 4 patients re-presented to hospital with abdominal pain, 1 with a common hepatic duct injury, 3 with deranged LFTs but no evidence of CBDS on ultrasound or MRCP and all 3 patients responded to conservative management

Soper,N.J. & (1992)

Population	**Category:** Symptomatic gallbladder stones **Number randomised:** 115 **Inclusion criteria:** Consecutive patients undergoing attepted laparoscopic cholecystectomy. Patients were eligible for inclusion of they were candidates for general anaesthesia, laparoscopy and cholecystectomy. **Exclusion criteria:** Patients with compelling reasons for or against intraoperative cholangiography were excluded: pregnancy allergy to contrast material, previous ERCP +/- sphincterotomy, dilated common bile duct >6mm on ultrasound, choledocholithiasis on ultrasound, History of jaundice or pancreatitis, elevated serum enzyme levels, intraoperative findings of unclear anatomy, conversion to open cholecystectomy, dilated cystic duct >4mm, cystic duct stones. **Age:** 49 (unclear if this is mean or not) range= 22 to 81 **Gender:** 30 male, 85 female **Country:** USA
Procedure	Patients were randomised by a random numbers table. Randomisation took place during surgery.
Arms	**(1) laparascopic cholecystectomy + intra operative cholangiogram** N: 56 Description: A four puncture standard laparoscopic cholecystectomy approach was used with a video laparoscope placed through the unbilical port and three laparoscopic sheaths inserted in the right subchondrium for operative manipulation of the gallbladder and porta hepatis. A cholangiocatheter was inserted. Cholangiograms were obtained after catheterising the cystic duct with a ureteral catheter. The catheter was placed 1-2cm inside the duct and cholangioclamp jaws were were advanced over the incision and closed theerby preventing leakage of contrast material. When free flow of contrast material was not achieved, another catheter was placed through a needle guide or through an angiocathether, and anchored in place using a clip placed across the duct while flushing the catheter to ensure patency. Cholangiograms were obtained using diatrizoate meglumine while interrupting patient respiration. When there was no flow of contrast material into the duodenum, films were repeated after administering glucagon. If proximal intrahepatic ducts were not visualised, morphine sulphate was administered intravenously and the cholangiogram repeated with additional contrast material. IOC was unsuccessful in 3 patients **(2) laparoscopic cholecystectomy**

	N: 59 Description: As previously described. Instead of intraoperative cholangiography, a clip was placed across the junction of the gallbladder with the cystic duct, and a cystic ductotomy was made. The duct was 'milked' back towards the ductotomy to diagnose and remove cystic ducts. Cholangiography was performed if the cystic duct was >4mm in diameter.
Results	

Outcome	LC (n=59)	LC+IOC (n=56)	
Bile leak	0/59	0/56	
Bile injury	0/59	1/56	
Length of stay	Mean=1 (SD not reported)	Mean=1 (SD not reported)	
• Missed common bile duct stones	0/59	1/56	

4b.2 Laparoscopic cholecystectomy compared to conservative management

Vetrhus,M. et al. (2002, 2003, 2004 & 2005) & Schmidt,M. et al. (2011a & 2011b)

Population

Group 1

Category: Symptomatic gallbladder stones- complicated

Number randomised: 64

Inclusion criteria: Patients with acute cholecystitis defined as acute abdominal pain in the right subcostal or midline epigastric area with duration of more than 8 hours and tenderness on clinical examination in the upper right quadrant accompanied by signs of infalmmation on ultrasonography and in clinical biochemistry data. Recruited between October 1991 and May 2004.

Patients with suspected common bile duct stones and elevated liver function tests and/or a common bile duct cross section diameter of >6mm at ultrasound were investigated with ERCP (patients with CBDS were excluded).

Exclusion criteria: Under 18 or over 80 years of age, severe concommitant disease, suspected common bile duct stones, acalculous cholecystitis, patients with localised peritonitis suggestive of gallbaldder perforation or gangrenous cholecystitis.

Age: Median= 58 years (range= 22 to 77)

Gender: 27, 37 females

Group 2

Category: Symptomatic gallbladder stones- non-complicated

Number randomised: 137

Inclusion criteria: Patients with episodic abdominal pain attacks compatible with sympotomatic non complicated gallbladder stone disease recruited between October 1991 and April 1994. Symptomatic disease was defined as episodes of pain, commonly continuous, in the right subcostal or midline epigastric area lasting more than 30mins, with ultrasound signs of gallbladder stones and no clinical or laboratory indication of other causes of their symptoms.

Exclusion criteria: Patients were excluded if they had infrequent and/or minimal pain that needed only very occasional medication were not randomised. Patients with abdominal symptoms previously attributed to gallbladder stones (dyspepsia, flatulence, nausea etc.) were not assessed. Also those with defined exclusion criteria (age under 18 years or over 80 years, pregnancy, serious concommitant disease and suspected CBDS) were treated as the discretion of the surgeon.

	Age: Median= 50 years (range= 20 to 79) **Gender:** 25 male, 113 female **Country:** Norway
Procedure	Patients were randomised in blocks of 5 using sealed opaque numbered envelopes. All patients were treated with antibiotics and supportive care. After symptom resolution all patients were discharged.
Arms	**(1) Cholecystectomy** N: 31 (group 1 complicated stones) N: 68 (group 2 non-complicated stones) Description: Patients were put on a regular waiting list and operated as soon as capacity permitted. The study was initiated after the introduction of Laparoscopic surgery was introduced to Norway so the majority of patients had laparoscopic cholecystectomy. **(2) Observation** N: 33 (group 1 complicated stones) N: 69 (group 2 non-complicated stones) Description: After discharge, participants in this group were given information about the nature of their disease, and were asked to avoid food which from their experience provoked abdominal pain. No other food restrictions were imposed.
Results	**Group 1 Complicated stones (data obtained from Vetrhus 2003 paper)**

Outcome	Cholecystectomy (n=31)	Conservative management (n=33)	
Disease progression	3/31 a	12/33 a	
Requirement for additional intervention	0/31	10/33 b	
Readmission	3/31 c	4/33 c	
Length of stay	-	-	
Mortality	4/31	0/31	14 year mortality was also reported but not extracted

a Acute cholecystitis, CBDS, acute pancreatitis
b Cholecystectomy
c Admissions for biliary pain

Group 2 Non-complicated stones (data obtained from Vetrhus 2002 paper)

Outcome	Laparoscopic cholecystectomy (n=68)	Conservative management (n=69)	
Disease progression	1/69*	3/69 a	*unclear: paper reports denominator is 95 for LC group and 69 for conservative group which doesn't add up to n=137

	Requirement for additional intervention	0/68 b	35/69 b	
	Readmission	2/68 c	12/69* c	*unclear: paper reports 12/69 in text and 15/69 in table.
	Length of stay	-	-	
	Mortality	4/68 d	4/69 d	14 year mortality was also reported but not extracted

a Acute cholecystitis, CBDS, acute pancreatitis
b Cholecystectomy
c Admissions for biliary pain
d This outcome was taken from Vetrhus 2004 paper

	The study was published as 6 separate papers, a 7th paper (Vetrhus et al 2005) was also identified but not included as it focused on long term pain outcomes which were not outcomes of interest for this comparison.

4b.3 Laparoscopic cholecystectomy compared to cholecystsotomy

No evidence meeting the inclusion and exclusion criteria was found.

4b.4 Day case laparoscopic cholecystectomy compared to planned inpatient cholecystectomy

Barthelsson,C. et al. (2008)

Population	**Category:** Unclear **Number randomised:** 100 patients recruited from a hospital outpatient department **Inclusion criteria:** Ultrasonography documented cholelithiasis, scheduled for planned laparoscopic cholecystectomy, ASA I-II, 20 to 70 years old, able to understand and speak Swedish. Patients also needed caregiver support at home on the first night folowing laparascopic cholecystectomy. **Exclusion criteria:** Not stated **Age:** Outpatient group= 44 years (range= 22 to 68) Inpatient group= 45 years (range= 22 to 68) **Gender:** No significant differences between the groups due to gender (no data reported) **Country:** Sweden
Procedure	Five expereicenced surgons performed the surgery. Both groups of patients were treated and post operatively observed by the same staff at the outpatient surgery department until discharged or transferred to a hospital ward. Prophylaxis against post operative pain and nausea was given with 1g paracetamol and 50mg diclofenac pre operatively. LC was performed using a standard four-trocar technique with carbon dioxide insufflations. Intra operative cholangiography was routinely performed. A standardised anaesthetic protocol was utilised. Patients in both groups were discharged when they were able to meet standard discharge criteria (adequate pain control: VAS<4), able to ambulate, able to void and tolerate oral liquids. Upon discharge patients were provided with a 1 day supply of pain medications (diclofenac 50mg 3 times per day, paracetamol 1g four times per day, suppository keto-bemidone to be taken as prescribed if severe pain was experienced). Unclear how randomisation was done.
Arms	**(1) Day case (outpatient) laparascopic cholecystectomy**

N: 50
Description: Patients were admitted for surgery on the morning of the day of surgery and LC was performed before 11am. Post operative recovery was managed at the outpatient surgery department. This group was discharged after 5 to 6 hours of post surgical observation. After discharge, patients received a telephone call from a nurse at the outpatient departement on the evening of the day of surgery and the next morning. The patients were also provided with a phone number to the same nurse in case they had any questions during the first post operative night home.

9 patients did not receive surgery (medical reasons= 4, no gallstone symptoms= 2, no caregiver at home= 1, pregnancy= 1, sugery elsewhere= 1)

7 patients were excluded following surgery (converted to open surgery= 2, admitted for post operative nausea and vomiting= 2, did not respond at follow up= 3)

34 patients from this group were available for analysis

(2) Inpatient laparascopic cholecystectomy

N: 50
Description: Patients received the same regimen as the outpatient group, but left the outpatient surgery department after 2 hours of observation, spent the night at a hospital ward and were discharged the next morning.

7 patients in this group did not receive surgery (no gallstone symptoms =3, medical reasons= 2, surgery elsewhere= 2)

4 patients were excluded after surgery (converted to open surgery = 1, refused to stay overnight=1, refused prescribed medication=1, did not respond to follow up=1)

39 patients in this group were eligible for analysis

Results

• **Outcome**	**Day (outpatient) LC**	**Overnight (inpatient) LC**	
• Failed day case discharge	-	-	
• Readmission	1/34	0/39	
• Length of stay	-	-	
• Mortality	-	-	
• Quality of life (State trait anxiety inventory)			
- Pre operative	Mean= 33.0 (SD=8.6)	Mean= 35.5 (SD=11.2)	
- Day 1	Mean= 35.9 (SD=10.4)	Mean= 34.7 (SD=10.1)	
- Day 7	Mean= 31.3 (SD=9.4)	Mean= 29.9 (SD=9.0)	
• Quality of Life (Health Index)			
- Pre operative	Mean= 31.26 (SD=4.7)	Mean= 29.92 (SD=4.2)	
- Day 7	Mean= 31.59 (SD=4.8)	Mean= 30.74 (SD=4.4)	

The following outcomes were reported but not extracted

- Symptom frequency and distress questionnaire measured at day 1 and day 7 (nausea, vomiting, pain, shivers, fever, breathing difficulty, coughing, tiredness, sore mouth/throat, loss of appetite, diarrhoea, constipation, sleeping disturbances, reduced mobility, depression, anxiety, concentration difficulties, memory deficiencies). This questionnaire was developed to assess patients undergoing stem cell transplantation

	and so is not specific or relevant to this patient group. None of the items on this questionnaire were significantly different between the inpatient and outpatient groups except for significant differences in reduced mobility at day 1 between the two groups, and significant differences in sleeping disturbances at day 7 between the two groups. - Post operative pain measured on a 10cm VAS every evening from day 1-7. This has not been extracted as data are reported in graph format only and do not show measures of dispersion. There were no significant differences between perceptions of pain between the two groups at any time point.

Hollington,P. et al. (1999)

Population	**Category:** Unclear **Number randomised:** 150 were randomised, 131 were analysed (19 patients were excluded after randomisation: 9 withdrew from the trial, 7 day case patients were inadvertently admitted overnight due to clerical error, 3 patients had their operation delayed to the afternoon, needed simultaneous hernia repair, or did not have home nursing service available to them) **Inclusion criteria:** Patients presenting for elective cholecystectomy (unclear what the indication for cholecystectomy was) who had an ASA status less than IV, adequate motivation levels, a family member at home post operatively, resident within the catchment area of the facility. Motivation was subjective and assessed by the surgeon at the outpatient clinic. **Exclusion criteria:** Patients who were assessed as being at risk of conversion to open surgery (such as those with multiple upper abdominal surgical scars). **Age:** Median= 45 years Overnight Median= 49 years Day Range= 17 to 83 years **Gender:** 12 males, 59 females Overnight 13 males, 47 females Day **Country:** Australia
Procedure	Randomisation was performed by a member of nursing staff during patient assessment in the outpatient clinic. Randomisation was done using 200 cards (100 for each group) which had been shuffled and sealed in plain envelopes. All procedures were performed by consultant surgeons, senior registras or a supervised trainee from the general surgical units and no changes were made to their standard surgical technique nor the type of anaesthetic agent used. Operative cholangiograms were performed routinely.
Arms	**(1) Day case (outpatient) cholecystectomy** N: 60 Description: Patients were admitted to hospital on the morning of their operation which was scheduled to commence before midday. Patients were scheduled to leave hospital that evening after review to confirm suitability for discharge. This occurred a minimum of 4 hours postoperatively and were discharged if their pain and nausea were controlled and they were not drowsy and were able to ambulate. If these criteria were not met they were transferred to the overnight stay ward. Discharged patients were contacted (12%) or visited (88%) later that evening, as well as the next morning by home nursing services to assess comfort and mobility and administer antiemetics, narcotics or oral analgesia if required. **(2) Overnight (inpatient) stay cholecystectomy** N: 71 Description: Not described.

Results	• **Outcome**	**Day (outpatient) LC**	**Overnight (inpatient) LC**	
	• Failed day case discharge	11/60	0/71	
	• Readmission	2/60	3/71	
	• Length of stay	-	-	
	• Mortality	-	-	
	• Quality of life	-	-	

Johansson,M. et al. (2006)

Population	**Category:** Symptomatic gallbladder stones **Number randomised:** 107 (7 patients were excluded after randomisation because of acute admissions for acute cholecystitis). **Inclusion criteria:** Patients presenting for gallstone disease surgery between the ages of 18 and 70 years who lived less than 50km from the hospital, and patients randomised to day care must have an adult able to accompany them home and stay with them overnight. **Exclusion criteria:** ASA score of III or IV, extreme obesity, patients with extensive abominal surgery, those with a clincial suspicion of common bile duct stones or a history of acute cholecystitis or pancreatitis were considered unsuitable for outpatient surgery and were excluded. **Age:** Not stated **Gender:** Not stated **Country:** Sweden
Procedure	Randomisation was achieved by computer generated random numbers with stratification for sex, age and body mass index.
Arms	**(1) Day case (outpatient) laparoscopic cholecystectomy** N: 52 Description: Day case laparoscopic cholecystectomy: patients were admitted to the day centre on the day of surgery. After initial recovery in a dedicated recovery suite, patients were transferred to the day surgery unit where they were encouraged to mobilise and start oral intake if fully conscious and not nauseous. The operating surgeon reviewed patients before 18:00hours. Discharge was allowed if the patient required oral pain medication only, tolerated oral fluids, had passed urine spntaneously and felt confident at managing at home. On discharge each patient was given a 2 day supply of diclofenac, paracetamol, tramadol hydrochloride and metoclopromide to be taken as prescribed if required. Intraoperative cholangiography was available, and 43 patients in this group received it. CBDS were demonstrated in 3 patients **(2) Overnight (inpatient) laparoscopic cholecystectomy** N: 48 Description: Over night laparoscopic cholecystectomy: patients were admitted to the ward on the day of surgery. After surgery patients were observed in the recovery room until considered fit to return to the ward. The cirteria for discharge on the following day were the same as the day care group. Intraoperative cholangiography was available and 42 patients received it. CBDS were demonstrated in 1 patient.

Results	• **Outcome**	**Day (outpatient) LC**	**Overnight (inpatient) LC**	

	• Failed day case discharge	4/52 a	0/48	
	• Readmission	-	-	
	• Length of stay	-	-	
	• Mortality	-	-	
	• Quality of life (Psychological general well being index)			
	- Day 1	Mean= 91.8 (SD=14.4)	Mean= 96.2 (SD=17.7)	
	- Day 7	Mean= 98.2 (SD=15.9)	Mean= 102.6 (SD=18.1)	
	a bile duct injury (converted to open) x1, Adhesions (converted to open) x1, haematoma at port site x1, retained CBDS treated by ERCP the following day			
	HADS reported but not extracted: pre op, 1 day, 1 week seperately for anxiety and depression.			

Keulemans,Y. et al. (1998)

Population	**Category:** Symptomatic gallbladder stones **Number randomised:** 80 **Inclusion criteria:** Patients who were indicated for cholecystectomy due to symptomatic cholelithiasis (according to the Rome criteria), confirmed by ultrasound. Patients had to live no more than 50km from the hospital and were required to have an adult willing to accompany them home and to stay with them for at least 24hours. **Exclusion criteria:** ASA III and IV, patients older than 70 years, and patients with extensive previous abdominal surgery, clinical suspicion of bile duct stones, acute cholecystitis, and calcified gallbladder were excluded from the study **Age:** 39 years (range= 20 to 62) Day case 48 years (range= 19 to 65) Overnight stay Unclear if means or medians are reported. **Gender:** 12 males, 28 females Day case 6 males, 34 females Overnight stay **Country:** The Netherlands
Procedure	Patients were randomly allocated by opening a sealed envelope. Laparoscopic cholecystectomy was performed during the morning by a surgeon in training with an experienced surgeon as an assistant. Routine cholangiography was not performed.
Arms	**(1) Day case (outpatient) laparoscopic cholecystectomy** N: 40 Description: Day case patients were admitted on the day of their surgery. After surgery they were encouraged to mobilise and start oral fluids if they were consious and not nauseated. Inpatient admission was necessary for: acute cholecystitis found during surgery, conversion to open procedure, significant bleeding or bile leakage during surgery. **(2) Overnight (inpatient) laparoscopic cholecystectomy** N: 40 Description: A short stay ward was opened during this study. As a consequence the first 19 patient were admitted to hospital the day before their surgery for pre

	assessment, and the next 21 were admitted to the short stay ward on the day of surgery. After laparoscopic cholecystectomy patients were observed in the recovery room until fit enough to return to the surgical ward. Patients stayed in hospital for at least one night after surgery.
Results	• **Outcome** / **Day (outpatient) LC** / **Overnight (inpatient) LC** • Failed day case discharge: 3/37 / 0/37 • Readmission: 0/37 / 0/37 • Length of stay: - / - • Mortality: - / - • Quality of life (derived from EuroQol) - Week 1: 58 (2) a / 56 (2) a - Week 6: 75 (1) a / 73 (1) a a unclear if mean and standard deviation or not

Young. et al. (2008)

Population	**Category:** unclear **Number randomised:** 28 **Inclusion criteria:** Patients undergoing laparoscopic cholecystectomy aged 50 and under, ASA II or less, and who spoke English were approached in the preadmission clinic. **Exclusion criteria:** Not stated **Age:** Mean= 39 years range= 26 to 48 (day case), 40 years range= 21 to 50 (overnight) **Gender:** Majority were female **Country:** Australia
Procedure	Random assignment was used to randomise patients. How this was achieved is not stated. All patients and their carers were given a standard educational session in the preassessment clinic. Discharge information was given in the Day procedure unit or by ward nursing staff.
Arms	**(1) Day case (outpatient) laparoscopic cholecystectomy** N: 14 Description: Not described **(2) Overnight (inpatient) laparoscopic cholecystectomy** N: 14 Description: Not described
Results	• **Outcome** / **Day (outpatient) LC** / **Overnight (inpatient) LC** • Failed day case discharge: - / - • Readmission: 0/14 / 0/14

	• Length of stay	-	-	
	• Mortality	-	-	
	• Quality of life	-	-	

4c- Common bile duct stones

4c.1 ERCP with laparoscopic cholecystectomy compared to Bile duct exploration with laparoscopic cholecystectomy

Bansal,V.K. et al. (2010)

Population	**Category:** Common bile duct stones **Number randomised:** 30 **Inclusion criteria:** Patients with symptomatic gallstones and CBDS with a diameter more than 10mm **Exclusion criteria:** None stated **Age:** Single stage= 47.1 years Multi stage= 39.07 years **Gender:** Single stage= 4 males, 11 females Multi stage= 5 males, 10 females **Country:** India
Procedure	Randomisation was done using computer generated random number sequences in concealed envelopes with block randomisation design.
Arms	**(1) Laparascopic cholecystectomy + laparascopic bile duct exploration** N: 15 Description: Laparoscopic cholecystectomy was performed. Four ports were used with telescope at the umbilicus. Dissection began around Calot's triangle, cystic duct and cystic artery were were clipped and the gallbladder was partially dissected. BDE then began. A vertical incision was made over the common bile duct. An effort was made not to extend the choledochotomy above the cystic duct-common duct junction. The CBD was flushed with copious normal saline to flush out the stones and debris. Choledoscopy was performed using a flexible choledochoscope inserted throught he epigastric port. . A rigid nephroscope with three pronged forceps was used to remove adherent stones. A check choledochoscopy was done to ensure common bile duct clearance. **(2) Endoscopic bile duct clearance followed by laparoscopic cholecystectomy 6 weeks later** N: 15 Description: Endoscopic bile duct clearance. No details provided. Laparoscopic cholecystectomy was performed 4 to 6 weeks after ERCP. No further details are provided.
Results	

	• **Outcome**	**LC+ pre op ERCP (n=15)**	**LC+BDE (n=15)**	

	• Length of stay	Mean=4.0 (range= 2 to 11)	Mean= 4.2 (range= 3 to 9)	
	• >1 ERCPs required to clear duct	2/15	0/15	
	• Mortality	-	-	
	• Retained stones	-	-	
	• Failed procedure	4/15	1/15	
	• Conversion to open surgery	2/15	1/15	
	• Quality of Life	a	a	
	a VAS 24hrs after surgery			

Cuschieri,A. et al. (1999)

Population	**Category:** Common bile duct stones **Number randomised:** 300 **Inclusion criteria:** ASA I or II patients who were suspected or had proved ductal calculi based on clinical features (jaundice, recent acute pancreatitis), liver function tests (elevated bilirubin, alkaline phosphatase) and external ultrasound findings. Investigations such as CT was optional. **Exclusion criteria:** Not stated **Age:** Range= 18 to 89 years Two stage Range= 19 to 88 years Single stage **Gender:** 42 males, 108 females double stage 60 males, 90 females Single stage **Country:** UK, Italy, Spain. Australia, Portugal, The Netherlands
Procedure	A central randomisation centre coordinated the randomisation of patients. When the central office was notified of an eligible patient, the data manager checked the entry criteria and faxed the randomised option. Randomisation was by random numbers generator that allocated the treatment before the start of the trial. The paper extracted in this table refers to the final results of this study that were published in 1999. Preliminary findings were also published in 1996, but since the final paper incorporates the prelimiary findings the 1996 paper has been excluded (see Cuschieri et al (1996) Preliminary findings of multicentre propspective randomized trial coomparing two stage vs singe stage management. Surg Endosc 10 1130-1135).
Arms	**(1) preoperative ERCP and stone extraction + laparoscopic cholecystectomy** N: 150 Description: All patients underwent ERCP, and endoscopic stone extraction was perfomred if stones were identified. After ERCP, patients had laparoscopic cholecystectomy during the same hospital admission. The interval between the ERCP and LC was left up to the individual surgeon. In patients where ERCP had failed to clear the duct, LC was attempted with laparoscopic duct clearnace when necessary. **(2) intraoperative cholangiography + laparoscopic cholecystectomy** N: 150

	Description: Patients were managed by single stage laparoscopic cholecystectomy. Intraoperative cholangiography was compulsory in this group Laparascopic ductal stone clearance was attempted in all patients with documented ductal stones. The technique of ductal stone clearance was by the transcystic duct route (for small non-occluding stones) or by supraduodenal common bile duct exploration (for large occluding stones). The exct technique was left up to the individual surgeon, as was the course of action to be taken (i.e. conversion to open surgery or post operative ERCP) if laparoscopic ductal stone extraction was unsuccessful.
Results	• **Outcome** — **LC+ pre op ERCP (n=150)** — **LC+BDE (n=150)** • Length of stay — Median= 9 (range= 5.5 to 14) — Median= 6 (range= 4.2 to 12) • >1 ERCP required to clear duct — 7/150 — 8/150 • Mortality — 2/136 — 1 out of?? • Retained stones — - — - • Failed procedure — 7/136 — 1/133 • Conversion to open surgery — 8/133 (6%) — 17/133 (12.8%) • Quality of Life

Ding,G. et al (2014)

Population	**Category:** Common bile duct stones **Number randomised:** 221 **Inclusion criteria:** patients with CBDS demonstrated on MRCP, aged 16 to 70 years, clinical presentation with biliary colic with or without jaundice, serum elevation of one of the following enzymes: aspartate aminotransferase, alanine aminotransferase, glutamyl transpeptidase, alkaline phosphatase, total bilirubin; radiological findings suggestive of gallstones and concomitant common bile duct stones with abdominal ultrasound showing possible CBDS or a dilated >8mm duct. **Exclusion criteria:** active acute pancreatitis, pregnancy, septic shock, intrahepatic gallstones, malignant pancreatic or biliary tumours, prior sphincterotomy, unfit for anaesthesia and surgery, contraindications to MRCP and ERCP, liver cirrhosis, previous abdominal surgery, inability to give informed consent. **Age:** mean**=** 58.42 (SD=7.21) BDE group; Mean= 57.53 (SD=6.31) ERCP group **Gender:** 51.81% female BDE group; 58% female ERCP group **Country:** China
Procedure	Eligible patients were randomised into one of the two treatment groups- unclear how this was done. Both groups received antibiotics once, immediately before the procedures but not continued post operatively. All surgeries and endoscopies in both groups were performed by the same surgeon who has extensive experience with both endoscopic and laparoscopic management of cholelithiasis and CBDS
Arms	**(1) Laparoscopic cholecystectomy + bile duct exploration** N: 110

	Under general anaesthesia a 5 trocar method was used to access the abdominal cavity. A conventional approach to laparoscopic cholecystectomy was first taken with dissection of Calot's triangle. The cystic duct was then pulled laterally to facilitate exposure of the anterior wall of the CBDm and the CBD was then opened longitudinally for a distance of aprox 1 to 1.5cm using laparoscopic scissors. A 5mm flexible choledochoscope was the used to identiify CBD stones which were then removed by flushing with sterile saline, passing a stone basket, or electrohydraulic lithotripsy as necessary to clear the CBD. A T tube was then inserted into the CBD via the cholodochotomy. Cholangiography was performed 14 days later and T tube removed immediately if no residual CBDS were identified. IF resudula stones were identified they were removed through the T tube track using a choledochoscope. **(2) Pre operative ERCP + Laparoscopic cholecystectomy** N: 111 ERCP with endoscopic sphincterotomy was performed using general anaesthesia. CBDS were removed using a basket or balloon with laser lithotripsy added if necessary. An endoscopic nasobiliary drainage (ENBD) was then inserted and kept in place until LC. LC was performed 2 to 5 days later, depending on the patients condition. Surgery was delayed if unrinary amylase was elevated or significant abdominal pain was present. Four to five days after LC cholangiography was performed via the ENBD and was removed if no stones were seen.
Results	

Outcome	Pre op ERCP+LC (n=111)	LC+BDE (n=110)	
Length of stay	-	-	
ERCPs required to clear duct	-	-	
Mortality	0/111	0/110	
Retained stones	9/95	2/97	8-10 years later
Failed procedure	6/111	7/110	
Conversion to open surgery	1/111	3/110	
Quality of Life	-	-	

ElGeidie,A.A. et al. (2011a)

Population	**Category:** Common bile duct stones **Number randomised:** 226 (7 excluded due to conversion to open surgery) **Inclusion criteria:** Patients with suspected common bile duct stones based on positive ulatrasound, laboratory data, MRCP and intraoperative cholangiography. Patients were included if they satisfied the following criteria: aged between 16 and 80 years; clinical, radiological and laboratory evidence suggestive of biliary obstruction, MRCP findigs suggestive of choledocholithiasis, intraoperative cholangiogram findings of choledocholithiasis **Exclusion criteria:** Acute cholangitis, gallstone pancreatitis, ASA grades IV and V, suspected CBD malignacy, previous cholecystectomy, pregnancy, contraindications to MRCP or ERCP due to previous gastrectomy, contraindications to laparascopic surgery due to previous upper abdominal surgery and marked liver cirrhosis. **Age:** Mean= 32.5 years (range= 19 to 64) Bile duct exploration Mean= 29.2 years (range= 20 to 67) Endoscopic sphincterotomy **Gender:** 29 males, 86 females (bile duct exploration)

	31 males, 102 females (endoscopic sphincterotomy) **Country:** Egypt
Procedure	Randomisation took place in the operating theatre after intraoperative cholangiography was performed. Only those with IOC findings suggestive of CBDS were randomised. Randomisation was done using serially numbered, sealed opaque envelope technique. Envelopes were drawn and opened by a nurse not involved in the study. All procedures were performed by the authors who were experienced in both ERCP and laparoscopy.
Arms	**(1) Laparoscopic cholecystectomy + laparascopic bile duct exploration** N: 115 Description: A standard approach for laparoscopic cholecystectomy with four ports was used. The decision to proceed to trancystic CBD exploration or a choledochotomy was determined by anatomy of the ducts as well as size and location of the stone. Laparoscopic choledochotomy was preferred when the CBD was wider than 10mm, stones were >10mm in size or >4 stones. Completion cholangiography was was routinely performed in all patients after clearance of the CBD. Choledoscopy was not available therefore all LCBDE were performed under fluroscopic guidance. **(2) Laparoscopic cholecystectomy + Intraoperative endoscopic sphincterotomy** N: 111 Description: 'The technique of LC with intraoperative ERCP has been documented before' Intraoperative sphincterotmy was performed after removal of the gallbladder and closure of prot sites.
Results	

Outcome	**LC+ intra op ERCP (n=111)**	**LC+BDE (n=115)**	
Length of stay	Mean= 3.1 (range= 1 to 7)	Mean=2.2 (range= 1 to 9)	
ERCPs required to clear duct	-	-	
Mortality	0/111	0 out of?	
Retained stones	0/101	4/112	
Failed procedure	3/111	6/115	
Conversion to open surgery	-	-	
Quality of Life	-	-	

ElGeidie,A.A. et al. (2011b)

Population	**Category:** Common bile duct stones **Number randomised:** 198 **Inclusion criteria:** Patients with suspected CBDS who were admitted to hospital. Pre operative diagnosis was based on a combination of clinical assessement (biliary colic with or without jaundice), liver chemistry (Serum elevation of at least one of the following enzymes: aspartate amino transferase, alanine amino transferase, gamma glutamyl transpeptidase, alkaline phosphatase, total bilirubin), and abdominal ultrasound (Showing possible CBD stones or a dilated CBD >8mm). Patients meeting

	the inclusion criteria underwent MRCP and only patients with MRCP evidence of CBDS were included. **Exclusion criteria:** Patients without evidence of CBDS of MRCP, patients with cholangitis, pancreatitis, patients <18 years or >80 years of age, ASA IV and V, suspected CBD malignancy, previous cholecystectomy, pregnancy, contraindications to laparoscopic surgery as previous upper abdominal surgery and marked liver cirrhosis. **Age:** 27.5 (19 to 64) Preop ES+ LC 31.2 (20 to 67) LC+ Intraop ES Unclear if numbers are means and rnages or not **Gender:** 29 males, 71 females (preop ES+ LC) 25 males, 73 females (LC+ intraop ES) **Country:** Egypt
Procedure	Patients were randomised using the sealed envelope technique.
Arms	**(1) pre operative ERCP + laparoscopic cholecystectomy** N: 100 Description: A pancreatocholangioscope was inserted into the duodenum through the mouth. The papilla was cannulated through this punctum using sphincterotome or after doing needle knife fistulotomy when cannulation via the punctum was difficult. Cholangiogram was done. ERCP was performed with the patient in the supine position, but there were problems with cannulating the papilla in this position so most patients were turned into the prone position. Endoscopic sphincterotomy was was done if stones were found. Stones were removed by balloon catheter or basket. Stones >15mm were removed with mechanical lithotriptor during the session. After biliary tract irrigation, a second baloon occlusion cholangiogram was performed to ensure complete clearance of the CBD and competence of the cystic duct closure. When there were no endoscopic sphincterotomy complications, laparoscopic cholecystectomy was ordered within a few days during the same hospital admission. During LC a transcystic cholangiography was done to ensure a clear CBD. **(2) laparoscopic cholecystectomy + intraoperative ERCP** N: 98 Description: Laparoscopic cholecystectomy was performed. After division of the cystic artery and dissection of the cystic duct, transcystic cholangiography was performed. If transcystic cholangiography yeilded positive results, the cholecystectomy was completed in the usual way and the patient underwent intraoperative ERCP.
Results	NB Data in tables and text do not correspond- data extracted here are from table 2 in paper.

• **Outcome**	**LC+ pre op ERCP (n=100)**	**LC+ intra op ERCP (n=98)**	
• Length of stay	Mean=3 decimal place eg 3.0? (range= 2 to 11)	Mean=1.3 (range=1 to 4)	
• ERCPs required to clear duct	-	-	
• Mortality	0/100	0/98	
• Retained stones	0/100	0/98	

	• Failed procedure	5/100	2/98	
	• Conversion to open surgery	2/91	2/85	
	• Quality of Life	-	-	

Hong,D.F. et al. (2006)

Population	**Category:** Common bile duct stones **Number randomised:** 234 **Inclusion criteria:** Patients with choleithiasis and extrahepatic duct stones diagnosed by history, physical examination, ultrasonography, MRCP, or cholangiogram through cystic duct cannulation. **Exclusion criteria:** Not stated **Age:** Mean=48 (range= 15 to 82) Surgical bile duct exploration No details provided for the intraoperative ERCP group **Gender:** 28 males, 65 females surgical bile duct exploration No details provided for the intraoperative ERCP group **Country:** China
Procedure	Patients were randomised according to their identifying numbers.
Arms	**(1) Laparoscopic cholecystectomy + intraoperative endoscopic sphincterotomy** N: 93 Description: Laparoscopic cholecystectomy was performed using four trocars. The cystic duct was catheterised and IOC was performed. If ERCP was performed, LC was paused- pneumoperitoneum was cancelled and nasogastric tube removed. After ERCP was completed penumoperitoneum was created and a nasogastric tube was inserted to conitnue the laparoscopic cholecystectomy. If IOC yeilded a positive result intraoperative ERCP with endoscopic sphincterotomy was performed. ERCP was performed by a gastroenterologist. Pneumoperitoneum was cancelled and nasogastric tube removed. A pancreatocholangioscope was inserted into the duodenal descending segment through the mouth. ERCP was performed before endoscopic sphincterotomy. Small stones 5 to 8mm were cleared using saline irrigation using the cholangiographic catheter. Stones 8 to 15mm could be removed by basket or balloon catheter. Stones larger than 15mm were removed by mechanical lithotriptor during intraoperative endoscopic sphincterotomy. Endoscopic sphincterotomy was performed after ERCP and any irrigation, basket or balloon clearance, or lithotripsy. **(2) Laparoscopic cholecystectomy + laparoscopic bile duct exploration** N: 141 Description: Cholecystectomy was performed using 4 trocars. The cystic duct and anterior and posterior walls of the common bile duct were dissected. The distal cystic duct was clipped. Cannualtion of the cholangiogram catheter was proceeded from the small incision in the proximal cystic duct through the trocar on the right midclavicular line below the ribs. The catheter was fixed by clip. The trocar was removed and reinserted again for placement of the catheter attached to the outside of the trocar. If a extrahepatic duct stone was detected on preoperative ultrasonography, the anterior wall of the common bile duct was lifted using the dissection clamp. A small incision was made and the electric hook was used for hemastasis. After the Foley catheter or irrigation catheter was covered with a segment of silicone tube, it was inserted into the bile duct. Stones were flushed out or extracted . A cholangioscope was considered if stone removal failed. If CBD stones were suspected on clinical history or properative ultrasonography without demonstrated stones, a cholangiogram through the cystic duct

	was performed. The CBD was opened on positive cholangiography results. For sludge or stones smaller than 10mm in the CBD, irrigation through the catheter in the cystic duct was used in an attempt to clear the bile duct. If these procedures failed, opening of the CBD was suggested. Primary closure of the CBD using 3-0 Vicryl or T-tube placement was performed after stone removal. After closure a second colangiogram through the cystic duct or T-tube was performed. A 5 or 3mm cholangioscope was inserted into the CBD through the 10mm trocar in the subxyphoid region. A multiple instument guide gave the 3mm cholangioscope access to the CBD. The cholangioscope was connected to a monitor, and the stones were extracted by basket after the bilairy track was checked upward and downward. Antiobiotics were administered once preoperatively, then postoperatively for 1 or 3 days.
Results	

• **Outcome**	**LC+ intra op ERCP (n=93)**	**LC+BDE (n=141)**	
• Length of stay	Mean=4.25 (SD=3.46)a	Mean= 4.66 (SD=3.07)a	
• ERCPs required to clear duct	-	-	
• Mortality	0/93	0/141	
• Retained stones	1/93	3/141	
• Failed procedure	8/93	15/141	
• Conversion to open surgery	8/93	15/141	
• Quality of Life	-		

a presume mean and SD but this is not clear in the paper

Koc, B. et al (2013)

Population	**Category:** Common bile duct stones **Number randomised:** 120 (only 111 were available for analysis) **Inclusion criteria:** patients with gallstones and concomitant common bile duct stones, classic biliary like pain, at least 4 weeks after the acute symptoms, gallstones detected by ultrasonography, CBD diameter >8mm or CBD demonstrated by ultrasound/MR-MRCP, one of the following: interherpatic duct dilation as detgermined by US and MR-MRCP, Alkaline phosphatase/or gamma-glutamyl transferase levels >1.5 times the limit of normal, cholangitis and biliary pancreatitis diagnosed at the first reference. **Exclusion criteria:** clinical, radiological, or biochemical evidence of cholangitis and pancreatitis, evidence of cirrhosis, interhepatic gallbladder, liver mass or abcess, neoplasm, suppurative or necrotizing cholecystitis, gallbladder empyema, or perfomration, pregnancy, recurrent CBDS **Age:** mean= 53.2 (SD=17.2) **Gender:** 38 males, 73 females **Country:** Turkey
Procedure	Patients were randomised to one of the two treatment groups- unclear how this was done.

	ERCPs were performed by a surgeon who performs 600+ interventions per year. Operations were performed by 2 surgeons experienced in hepatobiliary surgery. All patients received antibiotics according to the institutions surgical site infection protocol.
Arms	**(1) Preop ERCP + LC** N: 54 ERCP was performed under moderate sedation. If CBDS were suspected at the time of ERCP, a sphincterotomy was performed so that stones could be extracted using a balloon catheter or basket. *Unclear when LC was performed- implied on a different day, but could have been on same day as ERCP* Patients underwent LC with general anaesthesia. A standard 4 port configuration was used. **(2) LC+BDE** N: 57 Operations began like standard LC and the Calot triangle dissected. The cystic artery was clipped and divided, then milked towards the gallbladder to displace stones into the gallbladder. A clip was squeezed on to the gallbladder side to prevent backslippage of gallstones. Intraoperative cholangiogram was used. Cholodochotomy was perfomed. Sones were retrieved by spontaneous evacuation while incising the bile duct. A catheter was passed through the CBD with irrigation and suction by a hypertonic saline solution. Basket and balloon extraction of stones was possible.
Results	

Outcome	Preop ERCP +LC (n=54)	LC+BDE (n=57)	
Length of stay (days)	6	3	
>1 ERCP required to clear duct	-	-	
Mortality	-	-	
Retained stones	3/54	2/57	
Failed procedure	3/54	2/57	
Conversion to open surgery	1/54	0/57	
Quality of Life	-	-	

Nathanson,L.K. et al. (2005)

Population	**Category:** Common bile duct stones **Number randomised:** 86 **Inclusion criteria:** Patients with suspected common bile duct stones who had undergone laparascopic cholecystectomy, intraoperative cholangiography and had a failed trans cystic duct clearance were randomised to intraoperative choledochotomy or post operative ERCP. **Exclusion criteria:** ERCP prior to referral for cholecystectomy, severe cholangitis or pancreatitis requiring immediate ERCP drainage, common bile duct diameter less than 7mm on operative cholangiography, bilioenteric drainage required in addition to stone clearance. **Age:** Mean= 59.6 years (range= 18 to 92) ERCP

	Mean= 56.1 years (range= 17 to 91) Choledochotomy **Gender:** 17 male, 28 female ERCP 16 male, 25 female Choledochotomy **Country:** Australia
Procedure	Randomisation was achieved by phone call to the trial centre available 24hrs a day.
Arms	**(1) Intraoperative choledochotomy** N: 41 Description: Choledochotomy was by supraduodenal exposure of the common bile duct and longitudinal incision to a length sufficient to easily deliver stones. Stone clearance was achieved using irrigation, Fogarty balloon sweeps and dormia basket deployment with flexible choledochoscopic guidance. Complete clearnace was finally checked using both choledochscopy and then proximal and distal flouroscopic cholangiography. **(2) Post op ERCP** N: 45 Description: ERCP occurred prior to discharge from hospital. ERCP clearance was performed with the assistance of an anesthetist. Side viewing duodenoscopes were used with standard needle knife papillotomes when precut papillotomy was required. Sphincter balloon dilation as an alternative to sphincterotomy was not allowed. Mechanical and extracorporeal shock wave lithotripsy was available.
Results	

• **Outcome**	**LC+ post op ERCP (n=45)**	**LC+BDE (n=41)**	
• Length of stay	Mean=7.7	Mean= 6.4	
• >1 ERCP required to clear duct	11/45	0/41	
• Mortality	-	-	
• Retained stones	2/45	1/41	
• Failed procedure	-	-	
• Conversion to open surgery	1/45	1/41	
• Quality of Life	-	-	

Noble,H. et al. (2009)

Population	**Category:** Common bile duct stones **Number randomised:** 91 **Inclusion criteria:** High risk patients (over 70 years of age, over 60 years of age with comorbidity, or those over 50 years of age with a body mass index greater than 40) with bile duct stones proven on radiographic imaging, or with strong evidence of them (dilated CBD on ultrasound and abnormal liver tests), who were fit to undergo general anaesthesia and cholecystectomy.

	Exclusion criteria: Previous endoscopic sphincterotomy, required emergency sphincterotomy for severe cholangitis or pancreatitis, had a Billroth II gastrectomy, or if they were unfit for anaesthesia and cholecystectomy. **Age:** ES+LC group= 74.3 years (Interquartile range= 70 to 78.9) Bile duct clearance group= 75.9 years (interquartile range= 70 to 80.8) **Gender:** ES+LC group= 22 male, 24 female Bile duct clearance group= 16 males, 28 females **Country:** UK
Procedure	An independent computer generated random number system was used to allocate treatment. Standard techniques were used, and all procedures were undertaken by one of two experienced biliary surgeons, or by experienced trainees under direct consultant supervision.
Arms	**(1) Pre operative ERCP+ laparoscopic cholecystectomy** N: 47 Description: ERCP was performed with patients in the prone position If stones were detected they were retrieved using a Fogarty balloon trawl, Dormia basket deployment, and judicious use of mechanical lithotripsy. Duct clearance was confirmed using balloon occlusion cholangiography. If the duct could not be cleared, then an internal biliary stent was placed until subseqent attempts. If bile duct stones were confirmed on cholangiography, then sphincterotomy was perfomed. If no bile duct stones were identified on the initial cholangiogram a sphincterotomy was not performed. Laparoscopic cholecystectomy was carried out on the next avaialble operating list after ERCP, usually the following week. LC was performed using a standard 4 port technique. After a wide local dissection of Calot's triangle, the bile duct was imaged with laparoscopic ultrasound and/or cholangiography to confirm ductal anatomy and ensure there were no bile duct stones present. If present, the surgeon attempted the surgeon proceeded duplication here? What did the surgeon do – attempt or proceed? to laparoscopic bile duct exploration (as per exploration group). Assuming a clear duct, cholecystectomy would be completed in the usual manner. Gallbladder retrieval bags and subhepatic drains were used selectively. Antibiotic prophylaxis with 750mg of iv cefuroxime was administered only if there was spillage of gallbladder contents during dissection. **(2) Laparascopic bile duct exploration during laparoscopic cholecystectomy** N: 44 Description: The gallbladder was approached as per ES+LC group, and bile duct exploration began. Once BDE was complete, the cholecystectomy was then completed and a drain was placed next to any choledochotomy. Antibiotic prophylaxis with 750mg of IV cefuroxime was given if a choledocotomy was made or if there was spillage of the gallbladder contents during dissection. Drains were left in place until the first post operative morning or until bile was no longer present withi the drainage bag. Once ductal stones had been confirmed the surgeon then decided whether a transcystic or transductal approach was the most appropriate. A larger bile duct diameter, larger stones, or multiple stones favoured a transductal approach. Cholecdochoscopy was performed with a three channel 3 or 5 mm choledochoscope through a transverse incision in the cystic duct or a vertical incision in the common bile duct. Intermittent irrigation with normal saline was used to provide clear field of view allowing stones to ebextracted by baskets, balloons and electrohydraulic lithotripsy. Very small stones were flushed transcystically through the sphincter of Oddi under ultrasound visualisation with the aid of 20mg of hycoscine-N-butylbromide given IV to relax the sphincter. Two passes up and down the duct with the choledochoscope confirmed duct clearance, which was then checked again with laparascopic ultrasound after clips had been applied to the cyctic duct or the choledochotomy had been closed

	with and absorbable suture. T-tube drainage was used very selectively in cases where multiple stones or fragments of stones had been removed or when the surgeon was not completely convinced of duct clearance. Biliary stents to protect the cholodochtomy were not employed.
Results	

• **Outcome**	**LC+ pre op ERCP (n=47)**	**LC+BDE (n=44)**	
• Length of stay	Mean= 3 (range= 2 to 7)	Mean=5 (range= 2 to 7)	
• ERCPs required to clear duct	-	-	
• Mortality	2/47a	5/44d	
• Retained stones	7/36b	1/44e	
• Failed procedure	14/47c	0/44	
• Conversion to open surgery	2/47	4/44	
• Quality of Life	-	-	

a Due to unrelated disease

b 6 detected during intervention and received additional bile duct exploration, 1 presented 6 months postoperatively

c 12 received bile duct exploration (incomplete stone extraction x10, stone missed by ERCP x 2), 2 had failed ERCP (straight to LC x1, declined intervention x1)

d due to unrelated disease X4, due to carcinoma of the pancreas

e 1 presented 2.3 years post operatively with recurrent stone

Rhodes,M. et al. (1998)

Population	**Category:** Common bile duct stones **Number randomised:** 80 **Inclusion criteria:** Patients undergoing cholecystectomy who had common bile duct stones detected at peroperative cholangiography Laparoscopic cholecystectomy was done with 4 ports, and cholangiography was always done. After cholangiography patients with common bile duct stones were randomised to bile duct exploration or ERCP **Exclusion criteria:** Not stated **Age:** Not stated **Gender:** Not stated **Country:** UK
Procedure	States patients were randomised but unclear what method was used.
Arms	**(1) Cholecystectomy +bile duct exploration** N: 40 Description: In patients with CBDS less than 9mm in diameter, a transcystic approach was taken. If this approach failed choledochotomy was done but only if the common bile duct was

	greater than 6mm in diameter. In patients with CBDS larger than 9mm or with stones in the common hepatic duct a choledochotomy was used. After choledochotomy the duct was closed after a pigtailed stent was placed across the ampulla or a t-tube inserted. If the intervention failed to clear the ducts, postoperative ERCP was done at the next available opportunity **(2) Cholecystectomy + post op ERCP** N: 40 Description: Post operative ERCP was done within 48hrs of surgery. In patients whom ERCP failed to clear the bile duct, ERCP was repeated 1 week later.
Results	

• **Outcome**	**LC+ post op ERCP (n=40)**	**LC+BDE (n=40)**	
• Length of stay	Mean= 3.5 (range= 1 to 11)	Mean= 1 (range= 1 to 26)	
• >1 ERCP required to clear duct	7/40	0/40	
• Mortality	-	-	
• Retained stones	-	-	
• Failed procedure	10/40	10/40	
• Conversion to open surgery	-	-	
• Quality of Life	-	-	

Rogers,S.J. et al. (2010)

Population	**Category:** Common bile duct stones **Number randomised:** 122 (10 patients were excluded after randomisation for protocol violations, 6 in the ERCP arm and 4 in the BDE arm) **Inclusion criteria:** ASA I or II patients with classic signs and symptoms of gallstone disease (clinical and/or laboratory data and/or radiographic imaging suggestive of cholecystitis, cholelithiasis, cholangitis, gallstone pancreatitis, choledocholithiasis). Patients were over 18 years of age, with classic biliary type pain, at least one episode in the last 6 months, ultrasound demonstration of cholecystolithiasis, likely choledocholithiasis (suggested by one of the following: CBD 6mm or larger in diameter on US or CT, interhepatic duct dilation as determined by US or CT, elevated serum bilirubin, alkaline phosphatase and/or lipase) **Exclusion criteria:** Patients without ASA I or II status, patients with suppurative cholangitis or clinically severe pancreatitis. **Age:** Mean= 44.6 years (SD= 1.9) ERCP Mean= 39.9 years (SD= 1.9) BDE **Gender:** 16 males, 39 females ERCP 17 males, 40 females BDE

	Country: USA
Procedure	Participants were randomised according to serially numbered , sealed, opaque envelopes. The envelopes were helad securely and sperately at one site by the principal investigator.
Arms	**(1) laparoscopic cholecystectomy + laparascopic bile duct exploration** N: 57 Description: Laparoscopic cholecystectomy was performed by one full time faculty member with fellowship training in laparoscopy. Cholangiograms were obtained flouroscopically by antegrade contrast flushing through the cystic duct. All flouroscopy was done by the principan author under the presence and concurrence of an ERCP endoscopist. When stones were detected or suspected by cholangiography, transcystic exploration was undertaken by balloon or basket with associated dilation of the sphincter of Oddi. After BDE, completion cholangiograms were obtained to confirm that all the stones were removed. After Choalngiography and BDE, the cystic duct was ligated and the gallbladder removed. **(2) Pre operative ERCP + laparoscopic cholecystectomy** N: 55 Description: All ERCPs were performed by one of the authors who was a full time faculty member and gastroenterology fellowship instructor, in the presence and concurrence of the principal author/surgeon. Patients were scheduled to undergo ERCP with moderate sedation, prior to the intended laparoscopy. Duodenal atony during ERCP was routinely achieved using intravenous glucagon. Endoscopic sphincterotomy was undertaken if choledocholithiasis was detected or suspected on ERCP. Gallstones were extracted using a balloon catheter or retrieval basket. Small bowel gas was aspirated endoscopically at the conclusion of ERCP. Laparoscopic cholecystectomy was performed as soon as technically feasible (i.e. following abdominal gas decompression) after ERCP.
Results	

• **Outcome**	**LC+ pre op ERCP (n=55)**	**LC+BDE (n=57)**	
• Length of stay	Mean= 6.6 (SD=4)	Mean= 5.3 (SD=3.2)	
• ERCPs required to clear duct	-	-	
• Mortality	-	-	
• Retained stones	-	-	
• Failed procedure	1/55	2/57	
• Conversion to open surgery	-	-	
• Quality of Life	-	-	

Sgourakis,G. & (2002)

Population	**Category:** Common bile duct stones

	Number randomised: 78 **Inclusion criteria:** Patients suspected of common bile duct stones based on high SGOT (aspartate trans aminase?), bilirubin, alkaline phosphatase and CBD diameter (greater than or equal to 10mm). **Exclusion criteria:** Not stated **Age:** 43 to 89 years **Gender:** 32 male, 46 female **Country:** Greece
Procedure	Unclear how randomisation was achieved
Arms	**(1) laparoscopic bile duct exploration + laparascopic cholecystectomy** N: 36 Description: Patients had bile duct exploration and laparoscopic cholecystectomy in one stage **(2) ERCP + laparascopic cholecysytectomy** N: 42 Description: ERCP and potential endoscopic sphincterotomy and duct clearance Laparoscopic cholecystectomy was done seperately as a second stage procedure.
Results	

• **Outcome**	**LC+ pre op ERCP (n=42)**	**LC+BDE (n=36)**	
• Length of stay	Mean= 9	Mean= 7.4	
• >1 ERCP required to clear duct	-	-	
• Mortality	1/42	1/36	
• Retained stones	1/42	1/36	
• Failed procedure	5/32	4/28	
• Conversion to open surgery	-	-	
• Quality of Life	-	-	

4c.2 ERCP with laparoscopic cholecystectomy compared to ERCP alone (gallbladder in situ)

Boerma,D. et al. (2002)

Population	**Category:** Common bile duct stones **Number randomised:** 120 (108 analysed; 6 withdrew, 6 were immediately lost to follow up) Patients were followed up for 2 years after sphincterotomy. **Inclusion criteria:** Patients who underwent sucessful endoscopic sphincterotomy and extraction of common bile duct stones who had radiologically proven stones in the gallbladder were eligible for inclusion. Complete clearance of the CBD was assured by sweeping it with a 1cm balloon from

	the hilar region to the dupdenum and subseqent control cholangiography. If the gallbladder was not opacified despite optimal filling of the proximal biliary treee, the cystic duct was judged to be non patent. **Exclusion criteria:** Patients unfit for surgery (ASA IV and V) **Age:** Cholecystectomy group= 60 years (Range= 24 to 80) Watch and wait group= 63 years (Range= 21 to 80) **Gender:** Cholecystectomy group= 20 male, 29 female Watch and wait group= 29 male, 30 female **Country:** The Netherlands
Procedure	Randomisation with stratification (for participating hospitals and age) was done by computer via an independent trial bureau.
Arms	**(1) Laparoscopic cholecystectomy** N: 49 Description: Laparoscopic cholecystectomy within 6 weeks after sphincterotomy **(2) Watch and wait** N: 59 Description: Wait and see policy after sphincterotomy with cholecystectomy on demand only. Anaesthesia: Not stated
Comments	Study states 'since initial endoscopic sphincterotomy was often done in an acute setting outside regular working hours, information about patients who were eligible for the trial but who were not randomly allocated was incomplete. However 66 of 120 patients were randomly allocated in one hospital; characteristics of these patients were compared to 71 patients who were prospectively evaluated in a study about policy after sphincterotomy, and they seemed to be similar.' Study was supported by a grant from the committee on guideline development AMC.
Outcomes	
Results	• **Outcome** / **ERCP + LC (n=49)** / **ERCP alone (n=59)** • Quality of life: a / a • Recurrence/disease progression: 1/49 b / 27/59 c • Additional intervention required: 0/49 / 28/59 d • Mortality: 0/49 / 0/52 • Length of stay e: Median= 7 (Range= 1 to 47) / Median= 9 (range= 3 to 42) a MOS 24 is reported but no summary statistics or measures of dispersion are reported b biliary event- cancer c Pain x18, 7x cholecystitis, 1x obstructive jaundice, 1x biliocutaneous fistula d Cholecystectomy x22, additional ERCP x 6 e assume total length of stay, unclear in paper
	Study reports that quality of life was measured using MOS-24 and that both groups has the same scores and both groups were 'normal'- no data relating to this outcome is provided.

Lau,J.Y. et al. (2006)

Population	**Category:** Common bile duct stones **Number randomised:** 178 **Inclusion criteria:** Patients who had already undergone endoscopic sphincterotomy and complete clearance of bile duct stones were randomised to cholecystectomy or gallbladder in situ if they fulfilled the following criteria: older than 60 years of age, received complete endoscopic sphincterotomy (free bile flow and passage of a fully bowed sphincterotome with a 25mm wire), radiological evidence of an intact gallbladder containing gallbladder stones, no previous hospitalisation for cholecystitis. Patients with cholangitis were included and received decompression of the bile duct by insetrting a nasobiliary catheter. **Exclusion criteria:** Evidence of intrahepatic stones, radiological evidence of recurrent pyogenic cholangitis, intercurrent malignancy with a limited life span, or deemed unfit for cholecystectomy (ASA IV or V). **Age:** Mean= 70.9 (SD= 7.2), Median= 70 (range= 60 to 87)- cholecystectomy group Mean= 71.6 (SD= 6.8), Median= 72 (range= 60 to 89)- gallbladder in situ **Gender:** 43 males, 46 females (cholecystectomy group) 49 males, 40 females (gallbladder in situ group) **Country:** China
Procedure	Randomisation was done with a computer generated random list.
Arms	**(1) Cholecystectomy** N: 89 Patients in this group underwent laparascopic cholecystectomy as soon as practical. Patients recovering from severe cholangitis and pancreatitis were allowed a period of convalescence before returning for surgery. **(2) No intervention** N: 89 Patients in this group received no further intervention.
Results	• **Outcome** / **ERCP + LC (n=89)** / **ERCP alone** • Quality of life / - / - • Recurrence/disease progression / 6/89 a / 21/89 b • Additional intervention required / 0/89 / 26/89 c • Mortality / 11/89 / 19/89 d • Length of stay (total) / Mean=12.5 (SD= 6.1) / Mean= 8 (SD=6.4) a Cholangitis x5, biliary pain x 1 b CBDS x 16, acute cholecystitis x5 c ERCP x16, Cholecystectomy x10 d Due to biliary sepsis x4
	Data relate to end of follow up which was a minimum of 32 months for all patients, but a mean of 65.5 months for the cholecystectomy group, and 58.5 months for the gallbladder in situ group.

4c.3 ERCP compared to conservative management

Acosta,J.M. et al. (2006)

Population	**Category:** Common bile duct stones - pancreatitis **Number randomised:** 61 **Inclusion criteria:** Patients with gallstone pancreatitis admitted to the emergency surgery service. Patients who satisfied the following inclusion criteria were included: Age over 18 years, symptoms consistent with gallstone pancreatitis and ampullary obstruction, admission within 48hrs of onset of symptoms, serum amylase or lipase levels at least 2 times the upper normal limit, serum bilirubin grater or equal to 1.4mg/dL, objective demonstration of gallstones, written informed consent **Exclusion criteria:** Patients were excluded if there was evidence of alcoholism or other causes of pancreatitis, severe cholangitis (as they require immediate biliary disobstruction), coagulation disorder, cirrhosis, contraindication to general anaesthesia, previous Billroth II procedure (as the acces to the ampulla may be uncertain). **Age:** Intervention group= 34 years (range= 20 to 81) Control group= 34 years (range= 19 to 87) **Gender:** Intervention group= 6 male, 25 female Control group= 9 male, 21 female **Country:** USA
Procedure	All patients received supportive treatment (antibiotics, analgesics, nasogastric tube aspiration, ultrasonography). Randomisation was done by a computer generated list and sealed envelopes.
Arms	**(1) Selective ERCP after 48 hrs** N: 31 Description: ERCP with or without endoscopic sphincterotomy was performed selectively within 48 hours from the onset of symptoms at the treating physicians discretion in patients with associated persistent jaundice or cholangitis. Elective cholecystectomy was carried out during the initial hospitalisation once the pancreatitis had subsided in most patients. Patients had ERCP in 12 to 24 hours unless there was evidence of spontaneous disobstruction (disobstructed patients were offered same treatment as control group). Endoscopic sphincterotomy was performed when there was evidence of obstructed ampulla **(2) ERCP within 48hrs if obstuction persisted** N: 30 Description: All patients received supportive treatment (antibiotics, analgesics, nasogastric tube aspiration, ultrasonography). Patients experiencing spontaneous disobstruction within 48hrs continued with supportive measures until the resolution of pancreatitis. Those who remained obstructed underwent ERCP between 24 and 48 hours from the onset of symptoms complemented with endoscopic sphincterotomy if obstruction was confirmed. Elective cholecystectomy was carried out during the initial hospitalisation once the pancreatitis had subsided in most patients. Supportive treatment was provided to all patients. ERCP was offered selectively at the clinicians discretion in patients with associated persistent jaundice or cholangitis. Endoscopic sphincterotomy was only performed when there was evidence of obstructed ampulla

Results

• Outcome	Conservative management +/- ERCP within 48hrs (n=30)	Conservative management +/- ERCP after 48hrs (n=31)	
• Mortality	0/30	0/31	
• Disease progression	1/30a	2/31b	
• Additional intervention			
- ERCP	17/30 c	9/31 d	
- Elective cholecystectomy	22/30	22/31	
• Length of stay	Mean=9 (range/SD not reported)	Mean=10 (range/SD not reported)	

a Residual CBDS with jaundice x1
b Cholangitis x1, recurrent pancreatitis x1
c 16 patients disobstructed spontaneously
d 22 patients disobstructed spontaneously

Fan,S.T. et al. (1993)

Population

Category: Common bile duct stones - pancreatitis
Number randomised: 195 (11 patients were excluded because biliary stones had been excluded as a cause of the attack x2, Bilroth II gastrojejunostomy x3, caused by ERCP x5, diagnosis made after cardiac arrest x1)
Inclusion criteria: Consecutive patients with acute pancreatitis (severe upper abdominal pain with or without radiation to the back and repeated vomiting, with a serum amylase concentration above 1000 IU per litre).
Exclusion criteria: Not stated
Age: Median= 63 years (range= 26 to 90) ERCP
Median= 66 years (range= 17 to 94) conservative
Gender: 44 males, 53 females (ERCP)
36 males, 62 females (conservative)
Country: Hong Kong

Procedure

Participants were randomly assigned to one of the treatment arms. No randomisation details are provided.

Arms

(1) Early ERCP
N: 97
Description: ERCP was performed in the standard manner with the goal of selective cannulation of the common bile duct and avoidance of the pancreatic duct.
If ERCP identified one or more stones endoscopic papilotomy was performed with a cutting needle for ampullary stones or a papillotome for common bile duct stones.
If stone removal was incomplete a nasobiliary catheter was inserted.
(2) Delayed ERCP
N: 98
Description: Unclear what conservative management entailed.
ERCP was performed after thae acute attack had subsided, unless the following signs prompted ERCP during the acute phase: rising fever, leukocytosis, and tachycardia; increasing jaundice or serum bilirubin concentrations; shock not responding rapidly to

	intravenous fluid therpay. Endoscopic papilotomy was performed when one or more stones were identified. Performed with a cutting needle for ampullary stones and a papilotome for bile duct stones.
Results	<table><tr><th>• Outcome</th><th>Early ERCP (n=97)</th><th>Conservative management + delayed ERCP (n=98)</th><th></th></tr><tr><td>• Mortality</td><td>5/97</td><td>9/98</td><td></td></tr><tr><td>• Disease progression</td><td>0/97</td><td>13/98 a</td><td>Labelled as ‘complications’ in the study</td></tr><tr><td>• Additional intervention</td><td></td><td></td><td></td></tr><tr><td>- ERCP</td><td>0/97</td><td>27/98 b</td><td></td></tr><tr><td>• Length of stay</td><td>-</td><td></td><td></td></tr></table> a acute cholangitis x 12, acute cholecystitis x 1 b Requiring urgent ERCP: cholangitis x 10, septicaemic shock x 10 organ failure x 7
	Separate data is also provided for subgroups of mild pancreatitis and severe pancreatitis

Folsch,U.R. et al. (1997)

Population	**Category:** Common bile duct stones - pancreatitis **Number randomised:** - **Inclusion criteria:** Pain in the upper abdomen, serum amylase or lipase 3 times higher than the upper normal limit, Signs of acute pancreatitis on ultrasound or CT scan, bilirubin level lower than 5mg per deciliter, ability to perform ERCP within 72 hours of pain, age over 18 years, biliary origin of pacreatitis (gallstones seen on ultrasound, or CT scans, or if two of the following were present: elevated alkaline phosphatase level over 125 U per liter, elevated alanine aminotransferase over 75 U per liter, or an elevated bilirubin level over 2.3mg per deciliter). **Exclusion criteria:** Pregnant, coagulation abnormalities, alcoholism or metabolic cause of pancreatitis, included in this study or another study simultaneously **Age:** Median= 63 years (range= 20 to 90) Early ERCP Median= 63 years (range= 15 to 93) Conservative **Gender:** 60 males, 66 females (Early ERCP) 36 males, 76 females (Conservative) **Country:** Germany
Procedure	Patients were randomly assigned to one of the two treatment arms by means of a stratified block procedure. 32 patients were found after randomisation to not meet the inclusion criteria (ERCP not performed within 72 hrs x 12, bilirubin level higher than 5mg x12, non biliary cause of pancreatitis x6, under the age of 18 x1, coagulation abnormalities x1). The patients remained in the study and their data were analysed on an intention to treat basis.
Arms	**(1) Early ERCP** N: 126 No details about ERCP are provided If stones were detectd in the common bile duct at ERCP, papillotomy was performed to extract them.

	(2) Conservative management +/- ERCP N: 112 Description: Replacement of fluid, electrolyte, and colloid losses according to the levels of urinary excretion and according to the observed values for the hematocrit, serum albumin concentration, central venous pressure, and pulmonary-artery wedge pressure; intravenous alimentation with glucose and lipids if indicated in a patient with prolonged course of disease; insulin therapy if blood glucose levels exceeded 200mg per deciliter; assisted ventilation if the partial pressure of oxygen could not be maintained at a level higher than 60mmHg with an oxygen mask; nasogastric suction only in the case of gastric paresis and ileus; and antibiotic therapy only if temperature rose above 39C. ERCP was performed within 3 weeks after randomisation if signs of biliary obstruction or sepsis developed (the patient had a temperature higher than 39C, an increase in serum bilirubin level of more than 3mg per deciliter within 5 days, or persisitant biliary cramps). After 3 weeks ERCP could be performed in any patient if indicated.
Results	

• **Outcome**	**ERCP (n=126)**	**Conservative management +/- ERCP (n=112)**	
• Mortality	14/126 a	7/112 b	
• Disease progression	46/126	64/112	
- *Cholecystitis*	*13/126*	*20/112*	
- *Jaundice*	*1/126*	*12/112*	
- *Cholangitis*	*17/126*	*13/112*	
- *Peritonitis*	*2/126*	*3/112*	
- *Sepsis*	*13/126*	*1 6/112*	
• Additional intervention	-	-	
- ERCP	0/126	22/112 e	
• Length of stay	-	-	

a As a direct consequence of biliary pancreatitis x 10
b As a direct consequence of biliary pancreatitis x 4

Hui,C.-K. et al. (2002)

Population	**Category:** Symptomatic gallbladder stones **Number randomised:** 111 **Inclusion criteria:** Patients admitted to the department of medicine for acute cholangitis with gallbladder stones. Acute cholangitis was defined as the presence of abdominal pain, fever, jaundice, and dilated common bile duct on ultrasound. **Exclusion criteria:** Patients were excluded if ERCP detected common bile duct stones, interhepatic choellithiasis, or malignant obstruction. **Age:** Endoscopic sphincterotomy= 68.9 years (SD=14.8) Control group= 72.3 years (SD=12.2) **Gender:** Endoscopic sphincterotomy= 27 males, 23 females Control group= 32 males, 29 females **Country:** China
Procedure	Patients were randomised to one of the two trial arms using a list of random numbers generated by a computer booking system.

Arms	**(1) No intervention control** N: 61 Patients in this arm received no further intervention after the initial diagnostic ERCP **(2) ERCP** N: 50 Description: Patients randomised to this group had no CBDS on initial diagnostic ERCP but had endoscopic sphincterotomy and the bile duct was trawled using a dormia style basket and balloon catheter to remove mud and debris in the CBD.
Results	

• **Outcome**	**ERCP (n=50)**	**Conservative management (n=61)**	
• Mortality	1/50	1/61	
• Disease progression	14/50a	9/61a	
• Additional intervention	-	-	
• Length of stay	Mean= 8.1 (SD=3.0)	Mean= 9.1 (SD=3.2)	

a recurrent cholangitis

Neoptolemos,J.P. et al. (1988)

Population	**Category:** Common bile duct stones - pancreatitis **Number randomised:** 121 **Inclusion criteria:** Consecutive patients with acute pancreatitis (serum amylase >1000 IU/l, accompanied by a comparable clinical picture). Within 24hours all patients underwent ultrasound and biochemical prediction for gallstones. Severity of disease was predicted using modified Glasgow criteria. **Exclusion criteria:** Pregnant, under 18 years of age, history of chronic alcoholism or acute alcohol intake, presence of an identifiable secondary cause of the attack of pancreatitis such as drugs, hyperlipidaemia, trauma or surgery. **Age:** Mean= 64.5, range = 20 to 85 (ERCP) Mean= 72 years, range= 30 to 96 (Conservative) **Gender:** 25 male, 34 female (ERCP) 27 male, 35 female (conservative) **Country:** UK
Procedure	Patients were stratified according to predicted severity of pancreatitis and randomised to one of the two arms (unclear how).
Arms	**(1) ERCP** N: 59 Description: Urgent ERCP was undertaken by one highly skilled endoscopist within 72hours of admission. Endoscopic sphincterotomy was undetaken only if CBDs were identified at the time of ERCP. **(2) Conventional management** N: 62 Conventional management. Patients in this arm were eligible for ERCP after the 5th day of admission if indicated.

Results	• **Outcome**	**ERCP (n=59)**	**Conservative management (n=62)**	
	• Mortality	1/59	5/62	
	• Disease progression	-	-	
	• Additional intervention	-	-	
	- Requirement for ERCP	0/59	14/62	
	• Length of stay	-	-	

Nitsche,R. et al. (1995)

Population	**Category:** Common bile duct stones - pancreatitis **Number randomised:** 138 (38 were excluded after randomisation because inclusion criteria had not been followed x22, because of insufficient documentation x16) **Inclusion criteria:** Acute biliary pancreatitis, pain in the upper abdomen, amylase or lipase more than 3 times the upper normal limit, bilirubin <5mg/dl, ERCP can be performed within 72 hours of onset of pain, **Exclusion criteria:** Obstructive jaundice, under 18 years of age, pregnant, coagulopathy, alcoholism or metabolic cause for pancreatitis, included in this or another study simultaneously. **Age:** Not stated **Gender:** Not stated **Country:** Germany
Procedure	Randomisation procedure not stated
Arms	**(1) ERCP** N: 48 Description: ERCP performed within 72 hours of onset of pain. Sphincterotomy and stone extraction were undertaken if bile duct stones were identified on ERCP **(2) Conventional treament +/- ERCP** N: 52 Description: Conventional management ERCP was undertaken only in the case of persistant biliary colic, septical fever >39C, increase in bilirubin level for more than 3mg within 5 days.Three weeks after randomisation ERCP was allowed in all cases. Sphincterotomy and stone extraction were undertaken if ERCP identified bile duct stones.

Results	• **Outcome**	**ERCP (n=48)**	**Conservative management (n=52)**	
	• Mortality	4/48 a	2/52 a	
	• Disease progression	9/48	28/52	
	• Additional intervention	-	-	

	- ERCP	0/48	10/52 b	
	• Length of stay	-	-	

a deaths due to biliary pancreatitis only (an additional 2 people died of unrelated causes but it is unclear which group they were in)

b increasing jaundice x2, sceptical? septic fever x4, biliary colic x2, increasing LFTs x1, at patients own request x1

Oria,A. et al. (2007)

Population	**Category:** Common bile duct stones - pancreatitis **Number randomised:** 103 (one patient was excluded from the conservative management group due to misdiagnosis) **Inclusion criteria:** All patients who presented to the emergency ward within 48hrs of the onset of gallstone pancreatitis. The diagnosis of pancreatitis was based on 1) acute upper abdominal pain, 2) serum amylase 3 times or more the upper limit of normal, 3) biliary lithiasis on admission ultrasound, 4) evidence of pancreatic inflammation on admission CT scan, 5) absence of other causes of acute pancreatitis. To be included, patients had a distal main bile duct diameter measuring 8mm or more on admission ultrasound combined with a total serum bilirubin of 1.20 mg/dl or more. **Exclusion criteria:** Serious comorbid conditions that precluded ERCP, under the age of 18 years, pregnant, acute cholangitis. **Age:** Mean= 49.9 years (SD= 17.4) ERCP group Mean= 44 years (SD= 17.7) Conservative management **Gender:** 16 males, 35 females (ERCP group) 13 males, 38 females (conservative management group) **Country:** Argentina
Procedure	All patients received supportive measures including IV fluids, oxygen, nasogastric intubation if necessary. Antibiotics to prevent acute cholangitis were also administered. Patients were randomised using the sealed envelope technique which were randomised in blocks of 50 and opened by a surgeon not involved in the study.
Arms	**(1) ERCP** N: 51 Description: Endoscopic sphincterotomy was performed if one or more main bile duct stones were found ERCP was also performed in the absence of bile duct stones when there was evidenc of insufficent bilairy drainage (incomplete drainage of the contrast material 30mis after injection) due to ampullary oedema. Stents were inserted in cases of incomplete stone removal and the ERCP was repeated 24hrs later. **(2) Conservative management** N: 52 All patients received conservative management. Unclear what this entalied.

Results	• **Outcome**	**ERCP (n=51)**	**Conservative management (n=52)**	
	• Mortality	1/51	3/52	
	• Disease progression	-	-	
	• Additional intervention			

	- ERCP	0/51	2/52 a	
	- Cholecystectomy	47/51	45/52	
	• Length of stay	-	-	
	a acute cholangitis x1, progressive jaundice x1			

Vracko,J. et al. (2006)

Population	**Category:** Symptomatic gallbladder stones **Number randomised:** 105 **Inclusion criteria:** Consecutive and unselected series of elderly patients over 65years of age with acute cholecystitis. **Exclusion criteria:** None **Age:** Mean= 78 years (range= 65 to 101) **Gender:** 52 male, 53 female **Country:** Unclear- Sweden/Slovenia
Procedure	Patients were randomly assigned to treatment arms. Unclear how this was done.
Arms	**(1) Conservative treatment** N: 53 Description: Conservative treatment. Unclear what this entailed. **(2) ERCP** N: 52 Description: No details provided
Comments	Randomisation procedures not stated Results are difficult to read- tables are not clearly labelled and so not correspond with data written in text

Results

• **Outcome**	**ERCP (n=52)**	**Conservative management (n=53)**	
• Mortality	0/52	1/53	
• Disease progression	1/52a	16/52b	
• Additional intervention			
- ERCP	-	-	
- Elective cholecystectomy	38/52	28/53	
• Length of stay	c	c	

a Septic worsening of clinical course x1

b Sepsis (emergency surgery) x 15, Non septic worsening of clinical course x1

c Length of stay reported as number of people with a stay of 1-7, 8-14, 15-21 and >21

Zhou,M.Q. et al. (2002)

Population	**Category:** Common bile duct stones - pancreatitis

	Number randomised: 45 (6 of the patients had had a cholecystectomy before admission). **Inclusion criteria:** Patients admitted to hospital for acute gallstone pancreatitis (acute epigastirc pain, a history of gallstones, an increase in blood and urine amylase, cholelithiasis, choledochoectasia detected by ultrasound B or CT, diagnosed pancreatitis induced by caused other than alcohol, hypercalcinemia, hyperlipemia, trauma, etc. Patients with APACHE scores less then 8 were classified as mild pancreatitis. Patients with APACHE scores equal to or greater than 8 were classified as severe. **Exclusion criteria:** Not stated **Age:** 36 to 82 years **Gender:** 20 male, 25 female **Country:** China
Procedure	States patients were randomly divided into the study groups, but unclear how this was done. All patients were given traditional chinese medicine along with conventional supportive treatment.
Arms	**(1) ERCP** N: 20 Description: Patients received ERCP within 24hrs after admission. If stones in the common bile duct or stenosis of the inferior extremity or ampulla were found, such stones might be extracted. Endoscopic sphincterotomy was performed to extract calculi by basket. In case no calculi identified or multiple stones in a large diameter which were difficult to extract, nasobiliary drainage was carried out. If pancreatic infection or necrosis, or pyogenic cholangitis occurred, laparotomy was performed **(2) Conservative management** N: 25 Description: Not stated
Results	

• **Outcome**	**ERCP within 48hrs (n=20)**	**Conservative management (n=25)**	
• Mortality	-	-	
• Disease progression	-	-	
• Additional intervention	-	-	
- Laparotomy	0/20	3/25	
• Length of stay •	Mean= 8.5 (SD=2) mild Mean= 15.4 (SD=3) severe	Mean= 8.4 (SD=2) mild Mean= 63 (SD=4.8) severe	

4c.4 Biliary stent (uncleared bile duct) compared to cleared bile duct

Chopra,K.B. et al. (1996)

Population	**Category:** Common bile duct stones **Number randomised:** 43

	Patients were followed up for 30 months **Inclusion criteria:** Patients aged 70 years and older, or younger patients with a serious debilitating disease (according to ASA) with either a single bile duct stone greather than 10mm in diameter, or 2 or more stones of any size. To confirm the presence of CBDS all patients underwent ultrasound evaluation of the pancreatobiliary system before ERCP, which was done under antibiotic cover (IV antibiotics given 30mins prior to ERCP). Once confirmation of CBDS was achieved, patients were randomised to the study. **Exclusion criteria:** None stated **Age:** Stent group Median= 79 years (Range= 64 to 93) Duct clearance group Median= 77 years (Range= 59 to 93) **Gender:** Stent group= 24 males, 19 females Duct clearance group= 21 males, 22 females **Country:** UK
Procedure	Randomisation was done by a computer generated randomisation schedule using sealed envelopes.
Arms	**(1) Stent** N: 43 Description: Patients had a limited sphincterotomy (<0.75cm) followed by insertion of a 7F double pigtail endoprosthesis (Wilson Cook), the proximal tip of the prosthesis being placed proximal to the stone in the common bile duct and the distal end in the duodenum. No attempt was made to clear the bileduct stones. Patients were seen by a surgeon with a view to cholecystectomy. **(2) Duct clearance** N: 43 Description: Patients had a standard sphincterotomy (1.25 to 1.50cm) and an attempt was made to clear the bile duct by means of a dormia basket or balloon catheter with or without mechnaical lithotripsy. If after about 45 minutes this has proved unsuccessful, a 7F double pigtail endoprosthesis was inserted into the common bile duct to establish biliary drainage and the patient was scheduled for a further attempt of duct clearnace in a weeks time. Patients were seen by a surgeon with a view to cholecystectomy.

Results

• **Outcome**	**Stent**	**Duct clearance**	
• Mortality	4/43	2/43	
• Disease progression			
- Cholangitis	9/43	6/43	
- Pancreatitis	0	2	
- Perforation	1	0	
- Pyrexia	0	1	
- Gastrointestinal bleeding	2	1	
- Basket impaction	0	1	
- Respiratory insufficiency	0	2	
- Pulmonary embolism	0	1	
• Requirement for additional intervention	check		
- ERCP x 2	9/39	23/43	

	- ERCP x 3	3/39	9/43	
	- ERCP x 4	1/39	1/43	
	- Cholecystectomy	5/39	3/43	
	• Length of stay	-	-	

4c.5 Day case ERCP compared to planned inpatient ERCP

No evidence meeting the inclusion and exclusion criteria was found,

G.5 Included studies question 5

5a Early laparoscopic cholecystectomy compared to delayed laparoscopic cholecystectomy for acute cholecystitis

Gul et al (2013)

Population	**Number randomised:** 60 **Inclusion criteria:** Patients admitted with a diagnosis of acute cholecystitis (acute upper abdominal pain with acute right upper quadrant tenderness for more than 6 hours, associated nausea or vomiting, Fever, ultrasonography evidence such as distended gallbladder, presence of stones with a thickened edematous gallbladder wall, positive Murphy's sign, and pericholecystic fluid collection. In addition total leukocyte count >10,000mm3) in such patients was taken as an inclusive criterion for acute cholecystitis) **Exclusion criteria:** Patients with symptoms for more than 72 hours before surgery, patients with surgical jaundice (bilirubin level above 3.5mg/dl) ultrasound proved common bile duct stones, malignancy, preoperatively diagnosed gallstone pancreatitis, previous upper abdominal surgery, significant medical disease rendering them unfit for laparoscopic surgery, those who refused laparoscopic surgery **Age:** Mean=39.83 (8.25) Early; mean= 38.27 (9.82) delayed. Presume brackets contain standard deviation but this is not clear in paper **Male:female:** 12 male, 48 female **Country:** India
Procedures	**Surgeon:** Consultant general surgeon with extensive experience in laparoscopic surgery **Other interventions:** Some intraoperative modifications were adopted when necessary, such as decompression of the gallbladder, sutures to control cystic duct, placement of a closed suction drain. **Length of follow up:** 1 year **Drop outs:** none stated
Arms	All patients received initial supportinve treatment of intravenous fluids and intravenous antibiotics. Fluids, antibiotics and analgesics were also given post operatiely as required. **(1) Early** N=30

	Laparoscopic cholecystectomy was performed as soon as possible within 72 hours **(2) Delayed** N=30 After initial supportive treatment, patients were discharged when the acute attack subsided and were readmitted for elective laparoscopic cholecystectomy within 6 to 12 weeks.

Results

• **Outcome**	**Early LC**	**Delayed LC**	
• Readmission due to symptoms	-	-	
• Readmission due to surgical complications	-	-	
• Length of stay (total)	4.77 days	10.10 days	
• Mortality	-	-	
• Quality of life			
Mean VAS I hour	2.20 (SD= 0.847)	1.63 (SD=0.556)	
Mean VAS 12 hours	7.10 (SD= 1.863)	3.93 (SD=1.048)	
Mean VAS 24 hours	2.83 (SD= 0.834)	2.50 (SD=0.861)	
Mean VAS 48 hours	1.71 (SD=0.488)	1.52 (SD=0.574)	

Johansson,M. et al. (2003)

Population	**Number randomised:** 145 **Inclusion criteria:** Patients diagnosed with acute cholecystitis based on the finding of (1) acute right upper quadrant tenderness and ultrasound evidence of acute cholecystitis (presence of gallstones with thickened and edematous gallbladder wall, positive murphy's sign on ultrasound examination, and pericholecystic fluid collections); or (2) acute right upper quadrant tenderness, and ultrasound image showing the presence of gallstones, and one or more of the following: temperature above 38°C and/or leucocytosis greater than 10X10/L, and/or C-reactive protein level greater than 10mg/L **Exclusion criteria:** Patients were excluded if (1) they had bilirubin greater than 3.5mg/dl or (2) they had symptoms for more than 1 week, (3) if they were incapable of understanding written information regarding the study, or (4) if they were elderly (>90 years). **Age:** 58 (early) 55 (delayed) (SD: not reported) (Range: 22 to 88 (early) 20 to 81 (delayed) **Male:female:** 63% female (early) 57% female (delayed) **Country:** Sweden
Procedures	**Surgeon:** Consultants performed the operations. Fellow residents also participated in the study and operated under supervision. **Other interventions:** Operative cholangiography was performed routinely. **Length of follow up:** Until discharge from hospital **Drop outs:** 2 in the delayed group refused surgery and were excluded
Arms	**(1) Early cholecystectomy** N: 74 Description: Early cholecystectomy, performed within 48 hours of randomisation but

	not later than 7 days after onset of symptoms **(2) delayed cholecystectomy** N: 69 Description: Conservative management (with antibiotics, anti-inflammatory drugs, and intravenous fluids when required) and discharge from hospital when symptoms had abated. Patients were readmitted for elective surgery 6 to 8 weeks later. Patients were admitted one day before the planned operation and this day was included in the total hospital stay for this group. Patients who had worsening clinical signs or recurrence of acute cholecystitis before the planned surgery were treated with emergency laparoscopic cholecystectomy and classified as treatment failures.
Results	

• **Outcome**	**Early LC**	**Delayed LC**	
• Readmission due to symptoms	0/74	18/71 a	
• Readmission due to surgical complications	b	b	
• Length of stay (total)	5 (range= 3 to 63) c	8 (range= 4 to 50) c	
• Mortality	0/74	0/71	
• Quality of life	-	-	

a required emergency LC, unclear if this was during the index admission or as a readmission during the waiting period.
b 6 patients had bile leaks which were treated with ERCP. Unclear if this was during the planned stay or as a readmission
c unclear if this is mean or median

Kolla (2004)

Population	**Number randomised:** 40 **Inclusion criteria:** Patients diagnosed with acute cholecystitis based on a combination of clinical (acute right upper quadrant tenderness, temperature exceeding 37.5°C, and white blood count greater than 10 x 109/l) and ultrasonographic criteria (thickened, edematous distended gallbladder; positive sonographic Murphy's sign; presence of gallstones; and pericholecystic fluid collection). A 99Tc hepatoiminodiaceticacid scan was done in equivocal cases. **Exclusion criteria:** Patients with symptoms for more than 96h, previous upper abdominal surgery, coexisting common bile duct stones, or significant medical disease rendering them unfit for laparoscopic surgery were excluded from the study. **Age:** Mean= 41.5 (early), 38.6 (delayed) **Male:female:** 3:17 (early) 5:15 (delayed) **Country:** India
Procedures	**Surgeon:** Surgery was performed by consultant surgeons. **Other interventions:** Intraoperative cholangiogram was not performed. **Length of follow up:** Until discharge from hospital **Drop outs:** None
Arms	**(1) Early cholecystectomy** N: 20 laparoscopic cholecystectomy, performed within 24hrs of randomisation **(2) delayed cholecystectomy** N: 20

	laparoscopic cholecystectomy (performed at a mean interval of 68 days, range= 48-140 days after initial admission): conservative treatment with intravenous fluids and antibiotics were given. Patients who responded to conservative treatment underwent an elective laparoscopic cholecystectomy 6 to 12 weeks after the acute episode had subsided. Patients who did not respond to conservative treatment were treated with emergency open cholecystectomy.
Results	<table><tr><th>• Outcome</th><th>Early LC</th><th>Delayed LC</th><th></th></tr><tr><td>• Readmission due to symptoms</td><td>0/20</td><td>0/20</td><td></td></tr><tr><td>• Readmission due to surgical complications</td><td>-</td><td>-</td><td></td></tr><tr><td>• Length of stay (total)</td><td>Mean= 4.1 (range= 2 to 20)</td><td>Mean= 10.1 (range= 5 to 23)</td><td></td></tr><tr><td>• Mortality</td><td>0/20</td><td>0/20</td><td></td></tr><tr><td>• Quality of life</td><td></td><td></td><td></td></tr></table>
	• For the outcome 'mean post operative stay' the text reports a p value (p=0.952) which is different to that listed in the corresponding table (p=0.161)

Lai,P.B. et al. (1998)

Population	**Number randomised:** 104 **Inclusion criteria:** Patients diagnosed with acute cholecystitis based on clinical (acute right upper quadrant tenderness, temperature>37.5°C, and white blood cell count greater than 10X109/L) and ultrasonographic evidence (presence of gallstones in a thickened oedematous gallbladder positive Murphy's sign, and pericholecystic fluid collections). **Exclusion criteria:** Patients were excluded if they had symptoms for more than 1 week, had previous upper abdominal surgery, had significant medical diseases that rendered them unfit for laparoscopic surgery, or had coexisting bile duct stones with ductal dilation, acute cholangitis, or acute pancreatitis. **Age:** 55.8 (early) 56.1 (delayed) (SD: 14.6 (early) 14.4 (delayed)) (Range: Not reported) **Male:female:** 23:30 (early) 15:36 (delayed) **Country:** Hong Kong
Procedures	**Surgeon:** Surgery was performed by a group of 8 surgeons who each had performed over 50 cases. **Other interventions:** Intraoperative cholangiography was not performed routinely **Length of follow up:** Until discharge from hospital **Drop outs:** None
Arms	**(1) Early cholecystectomy** N: 53 Description: laparoscopic cholecystectomy performed within 24hours of randomisation **(2) Delayed cholecystectomy** N: 51 Description: laparoscopic cholecystectomy- conservative treatment with intravenous fluid, and antibiotics. Patients who responded to conservative treatment had elective laparoscopic cholecystectomy 6 to 8 weeks after the acute episode had subsided. Patients were routinely admitted one day before the operation. Patients with worsening

	clinical signs or those who developed a recurrent attack of acute cholecystitis before the elective surgery were treated with emergency laparoscopic cholecystectomy.
Comments	Notes on outcomes: Some patients in the delayed group had an outcome "defaulted surgery after sucessful conservative treatment'. Unclear if the data reported in the paper includes or excludes the 5/51 who defaulted surgery.
Results	

• **Outcome**	**Early LC**	**Delayed LC**	
• Readmission due to symptoms	0/53	8/51 a	
• Readmission due to surgical complications	b	b	
• Length of stay (total)	Mean= 7.6 (SD= 3.6)	Mean= 11.6 (SD= 3.4)	
• Mortality	0/53	0/51	
• Quality of life	-	-	

a required emergency LC, unclear if this was during the index admission or as a readmission during the waiting period.
b postoperative complications are reported but unclear if these were dealt with during the procedure or whether patients were readmitted

Lo,C.-M. et al. (1998)

Population	**Number randomised:** 99 **Inclusion criteria:** Patients diagnosed with acute cholecystitis based on the following three criteria: acute upper abdominal pain with tenderness in the right costal margin, fever >37.5°C, leucocytosis of 10 X 109/L, or both; and fever >, and ultrasound confirmation of acute cholecystitis (presence of gallstones, thickened gallbladder wall, edematous gallbladder wall, pericholecystic fluid collection, ultrasonic Murphy's sign). **Exclusion criteria:** Patients contraindicated for LC were excluded before randomisation (spreading peritonitis or uncertain diagnosis, previous upper abdominal surgery, absolute contraindications for surgery, concomitant malignant disease or pregnancy, conservative treatment for 72 hours before the diagnosis was made, refused surgery, had symptoms for more than 7 days before admission) **Age:** 59 (early) 61 (delayed) (SD: Not reported) (Range: 20 to 83 (early) 27 to 87 (delayed)) **Male:female:** 26:19 (early) 21:20 (delayed) **Country:** China
Procedures	**Surgeon:** Surgery performed by one of two surgeons with previous experience of over 300 laparoscopic cholecystectomies (early and delayed) **Other interventions:** Selected patients with suspicions of common bile duct (CBD) stones were subject to preoperative ERCP. When CBD stones were discovered, endoscopic sphincterotomy was performed and ductal clearance achieved before surgery. Interoperative cholangiogram was not routinely performed. All patients received the same supportive treatment during the acute phase (intravenous fluids and antibiotics, nasogastric suction catheters and urinary catheters

	were used when clinically indicated). **Length of follow up:** Patients were seen in surgical outpatients clinic 1 and 4 weeks post discharge **Drop outs:** 4 (early, 1 refused surgery, 3 misdiagnosed) 9 (delayed, 5 refused surgery, 1 lost to follow up before surgery, 1 contraindicated for surgery, 2 misdiagnosed)
Arms	**(1) Early cholecystectomy** N: 45 Description: laparoscopic cholecystectomy performed as soon as possible within 72 hours of admission **(2) Delayed cholecystectomy** N: 41 Description: laparoscopic cholecystectomy- initial conservative treatment and discharge as soon as the acute attack subsided. Subsequent readmission for elective laparoscopic cholecystectomy 8 to 12 weeks later. Recurrent symptoms before elective surgery were treated conservatively whenever possible. Conservative treatment was considered to have failed when two surgeons considered early operative intervention to be mandatory because of the presence of spreading peritonitis, persistent fever, or increasing gallbladder mass.
Results	• **Outcome** / **Early LC** / **Delayed LC** • Readmission due to symptoms: 0/45 / 7/33 a • Readmission due to surgical complications: - / - • Length of stay (total): Median= 6 (range=2 to 16) / Median= 11 (range=5 to 33) • Mortality: 0/45 / 0/41 • Quality of life: - / - a Biliary colic x1, cholecystitis x4, acute cholangitis x2. An additional 8 patients in this group failed to respond to conservative treatment and underwent urgent LC at a median of 63 hrs after admission (hence the smaller denominator for this outcome).

Macafee,D.A. et al. (2009)

Population	**Number randomised:** 72 **Inclusion criteria:** Patients aged 18 to 80 years presenting with biliary colic or acute cholecystitis and admitted as an emergency. **Exclusion criteria:** Patients who had a co morbidity deeming them unfit for laparoscopic cholecystectomy, those previously diagnosed with gallstone disease, those with deranged liver function tests, acute pancreatitis, or ascending cholangitis, and those unable to understand the implications of the trial or give informed consent were excluded. **Age:** Median age 52 (early) Median age 53 (delayed) (SD: Not reported) (Range: 21 to 80 (early) 26 to 80- (delayed)) **Male:female:** 10:26 (early) 15:21 (delayed)

	Country: UK
Procedures	**Surgeon:** A consultant was present at all operations but competent trainees were allowed to perform the operation under supervision **Other interventions:** On table cholangiography was used only when necessary. **Length of follow up:** Participants received telephone follow up from a nurse practitioner 2 weeks after the operation. One of the two main surgeons had further telephone follow up between postoperative days 30 and 35 when outcome data were collected **Drop outs:** None
Arms	**(1) Early cholecystectomy** N: 36 Description: laparoscopic cholecystectomy within 72 hours of recruitment Timing: Early **(2) Delayed cholecystectomy** N: 36 Description: managed with analgesia, intravenous fluids, and antibiotics as indicated clinically; once recovered from the acute illness they were discharged home and a date was arranged for readmission for elective laparoscopic cholecystectomy 3 months later. Timing: Late **(3) -** N: 0
Comments	Source of funding: UK NHS Culyer funding Additional comments: Further health economic data reported in the paper but not extracted for clinical evidence (may be used in separate health economic analyses)
Results	

• **Outcome**	**Early LC**	**Delayed LC**	
• Readmission due to symptoms	0/36	3/36	
• Readmission due to surgical complications	-	-	
• Length of stay (total)	Median=6 (range=2 to 20)	Median=6 (range= 2 to 17)	
• Mortality	-	-	
• Quality of life EQ-5D (non imputed value)	Mean= 0.85 (SD= 0.26)	Mean= 0.93 (SD= 0.13)	

Yadav,R.P. et al. (2009)

Population	**Number randomised:** 50 **Inclusion criteria:** Patients diagnosed with acute cholecystitis presenting within 7 days of onset. Diagnosis was based on a combination of clinical, ultrasonographic, and laboratory tests (clinical criteria included at least 3 of the following: right upper quadrant pain, Murphy's sign, tenderness in the right hypochondrium, local signs of peritonitis, and fever [temperature>100°F]) **Exclusion criteria:** Patients presenting with AC more than 7 days duration, those with common bile duct stones or ductal dilation, patients with serious medical disease for whom surgery was inappropriate were excluded.

	Age: Mean=42.68 SD: 14.18 (early) Mean= 40.26 SD:11.62 (delayed) **Male:female:** 12:38 **Country:** Nepal
Procedures	**Surgeon:** The same consultant performed all operations in both groups **Other interventions:** None stated **Length of follow up:** 12 months **Drop outs:** None
Arms	**(1) Early cholecystectomy** N: 25 Description: managed with intravenous fluids, antibiotics, injection tramadol in postoperative period and were posted for laparoscopic cholecystectomy as soon as possible. **(2) Delayed cholecystectomy** N: 25 Description: managed with intravenous fluids, antibiotics and injection diclofenac sodium for two days, followed by oral antibiotics and analgesics for the next 5 days. They were discharged from hospital after complete relief of symptoms and were called for laparoscopic cholecystectomy after 6 to 8 weeks.
Results	• **Outcome** / **Early LC** / **Delayed LC** • Readmission due to symptoms: - / - • Readmission due to surgical complications: - / - • Length of stay (total): Mean= 4.33 (SD= 1.46) a / Mean= 7.23 (SD= 1.63) a • Mortality • Quality of life a Excludes patients converted to open surgery

5b Early laparoscopic cholecystectomy compared to delayed laparoscopic cholecystectomy for common bile duct stones

Reinders (2010)

Population	**Number randomised:** 96 **Inclusion criteria:** Patients over the age of 18 years who underwent successful endoscopic sphincterotomy and stone extraction for choledocholithiasis and who had radiologically proven residual gallbladder stones. **Exclusion criteria:** Patients unfit for surgery (ASA III IV), patients with biliary pancreatitis or acute cholecystitis **Age:** Median= 55 Early Median= 47 Delayed (SD: not stated) (Range: 21 to 85 years) **Male:female:** 11 males, 36 females Early

	18 males, 29 females Delayed **Country:** The Netherlands
Procedures	**Randomisation:** Randomisation was done through consecutive, closed, opaque envelopes. **Surgeon:** Not stated **Other interventions:** Not stated **Length of follow up:** 6 months after surgery **Drop outs:** 2 patients were wrongly randomised an excluded from analysis
Arms	**(1) Early laparoscopic cholecystectomy** N: 47 Description: Laparoscopic choelcystectomy within 72 hours after endoscopic sphincterotomy **(2) Delayed laparoscopic cholecystectomy** N: 47 Description: Laparoscopic cholecystectomy 6 to 8 weeks after endoscopic sphincterotomy Timing: Late
Comments	Source of funding: Not stated
Results	

• **Outcome**	**Early LC after ERCP (n=47)**	**Delayed LC after ERCP (n=47)**	
• Readmissions			
• Recurrent symptoms	1/47 a	18/47 b	
• Surgical complications			
- Post ERCP	3/47 c	1/47 d	
- Post cholecystectomy	6/47 e	6/47 f	
• Length of stay (total)			
- Post operative	Median= 1.50 (range= 1 to 16)	Median= 2.00 (range= 1 to 11)	
- Total	Median= 5.00 (range= 2 to 20)	Median= 5.00 (range= 2 to 18)	
• Mortality	0/47	0/47	
• Quality of life	g	g	
•			

a 1x recurrent CBDS
b 13 x colic pain, 4 x cholecystitis, 1 recurrent CBDS
c 2 x post ERCP pancreatitis, 1 x duodenal perforation
d 1 x post ERCP pancreatitis
e 3x cystic stump leakage, 1x haemorrhage, 1x wound infection, 1x abscess
f 1x cystic stump leakage, 5x wound infection
g VAS pain scores reported

G.6 Included studies question 6

Table 1: Barthelsson (2003)

Study description	**Qualitative study to explore patients experiences of laparoscopic cholecystectomy** The study was conducted in the day surgery department of a University hospital. Patients were recruited from the outpatient surgery department. A purposive sample of 12 patients was selected during their preoperative visit, one week prior to laparoscopic cholecystectomy. Interviews took place 1 week after the operation. **Age**: range from 28 to 60 years **Sex:** 2 males, 10 females **Country**: Sweden
Inclusion/exclusion criteria	Only ASA I to II patients were included. They also had to fulfil the criteria for discharge from the day surgery department (be able to drink, void and not be in pain). A relative must also have been present to accompany them home after discharge.
Methodology	Patients were interviewed one week after their operation. The interviews lasted approximately 45 minutes. The interviews began with the question "How did you experience having keyhole cholecystectomy at the day surgery department". After that participants could talk freely. The interviewer only posed clarifying questions.
Analysis	Following recommendations from Lincoln & Gruba (1985) data collection was concluded when facts started to be repeated and when the researcher noticed that themes and examples are no longer being expanded upon. This occurred after 12 interviews. Categories and subcategories of text were created through the repeated reading of meaningful text. Sentences were coded and important phrases and sensory impressions that arose were recorded. Quotations were used to provide additional elucidation.
Results	**Wounds** Respondents had many questions about how their wounds should be cared for and how the wounds should normally look "*what should the wounds look like? One wound is still gaping open…How long does it take before the stitches fall out, and can I work?"* **Lack of information** Several respondents had no memory of the information given by the surgeon on discharge from hospital "*I don't remember anything from the discharge information, only that a surgeon stood by the bed and talked. I only remember what was on the information sheet. I wander: Was it the gallbladder? Were there stones? Did the operation go well*?"

Table 2: Blay (2005)

Study description	**A randomised trial of different types of patient information, with a survey of patient opinions.** 128 patients who attended the pre admission clinic for laparoscopic cholecystectomy were recruited. 12 participants were lost to follow up and 8 were withdrawn from the surgical waiting list. Therefore 93 patients were followed up post operatively. **Age**: mean= 49.1 years (standard), 60 years (educational intervention) **Sex:** 15 males, 78 females **Country**: Australia
Inclusion/exclusion criteria	Patients were excluded if they were booked for day surgery, or if they were under 14 years of age.
Methodology	A randomised trial with a post-operative survey of patients having laparoscopic cholecystectomy. Patients were randomly assigned using randomisation tables to standard preadmission information provided by pre assessment clinic staff, or to standard information plus education intervention. **Standard information**: not described **Standard information plus education intervention**: verbal and written information on pain management, wound care, diet, bowel management, and management of medical complications. There was an opportunity for patients to ask questions. Participants were followed up at one day, and 2 weeks post surgery.
Analysis	Pre and post operative questionnaires were compared.
Results	**Requested information topics and the numbers of participants by groups**

Topic	Standard information (n=23)	Educational intervention (n=10)
General information	8	1
Wound related	5	1
Pain management	7	0
Dietary advice	4	2
Bowel management	2	3
Nausea and vomiting	2	0
Activity	2	0
Medication	2	0

Table 3: Blay (2006)

Study description	**Survey to determine what information the pre admission clinic nurses provided to patients undergoing laparoscopic cholecystectomy** 100 patients booked for laparoscopic cholecystectomy participated in the study **Age**: Mean= 60.3 years (range= 1 month to 80 years). **Sex:** 21 male, 79 female **Country**: Australia
Inclusion/exclusion criteria	Not stated
Methodology	A nurse interviewed patients (using a preoperative questionnaire) after they had completed their preoperative assessment conducted by pre assessment clinic medical and nursing staff. A preoperative questionnaire was used to assess participants knowledge of laparoscopic surgery, post operative recovery.
Analysis	Results of the questionnaire were analysed using descriptive statistics only.
Results	**Diet** • 83% said they received no post-operative dietary advice, yet many were able to state foods that were best avoided • 3% requested additional information on diet **Activity** • 65% of patients had not been told about how long it would take to resume normal activities. • 6% of patients requested additional information on post operative activity **Lack of information** • 14% said they received no information from PAC nurse • Patients were not given definitive advice on how long they should expect to be in hospital **Information required** • Patients requested additional information on diet, self care after discharge, general preoperative information, postoperative activity, pain management, medical terminology.

Table 4: Tamahankar (2009)

Study description	**A survey of internet use amongst patients undergoing abdominal wall hernia repair, or laparoscopic cholecystectomy** 105 patients undergoing elective hernia repair or laparoscopic cholecystectomy were included. Maintaining usual practice, all patients were counselled about their operations in the outpatient and pre operative assessment clinic and standard trust information leaflets were provided without any mention of the study. **Age**: majority were >65 years **Sex**: predominantly male **Country**: UK
Inclusion/exclusion criteria	Not stated
Methodology	Participants completed a questionnaire on the morning of their operation on arrival to the ward
Analysis	Results of the questionnaire were analysed using descriptive statistics only.
Results	**Information required** • 31% of patients with internet access used it to acquire additional information about their operations and 58% used internet search engines to acquire additional information • Of the people who searched the internet regarding their operations, 79% rated the information they found as good or very good. 23% were confused or worried about by the information they received

Table 5: Young (2001)

Study description	**A randomised controlled trial of day case (n=14) versus overnight stay (n=14) cholecystectomy (N.B. this study is not included in the strategies for managing gallstone disease question as relevant outcomes were not reported)** **Age**: Mean= 39 years (day case), 40 years (overnight) **Sex**: predominantly female **Country**: Australia
Inclusion/exclusion criteria	Patients were less than 50 years of age and assessed as having ASA grading of 2 or less.
Methodology	A telephone survey took place on day 10 of recovery
Analysis	Results of the survey were analysed using descriptive statistics only.
Results	**Discharge instructions (patients)** 100% of day case patients agreed they had been given sufficient discharge information for recovery 44% of overnight stay patients agreed they had been given sufficient discharge information for recovery. **Discharge instructions (carers)** 100% of carers of day case patients stated they had sufficient discharge information 55.6% of carers of overnight stay patients stated they had sufficient discharge information **Overnight stay patients requested the following information** - Diet and fluids, what sort of meals/drinks eat/drink or when could normal diet/fluids be introduced - Pain management - Wound care, i.e. whether to bathe the wound. **Overnight stay carers requested the following information** - Diet and fluids, what sort of meals/drinks eat/drink or serving sizes the patient could eat/drink or when could normal diet/fluids be introduced - Pain management - Wound care, i.e. whether to bathe the wound.