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A Systematic Literature Review and Meta-analysis

Incidence and Predictors of Common Bile Duct Stones in Patients with Acute Cholecystitis

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Key words:

Acute cholecystitis; choledocholithiasis; common bile duct stone; common bile duct calculi

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ABSTRACT

Introduction: Acute cholecystitis (AC) is a surgical condition that is usually managed by emergency surgery. The presence of common bile duct stones (CBDS) in this setting mandates definitive treatment to avoid complications such as cholangitis. The incidence of CBDS in the setting of AC is poorly defined.

Methods: A systematic English literature search was conducted in PubMed, Medline and Embase to determine the incidence of CBDS in patients presenting with AC. Outlier studies identified by funnel plot analysis were excluded and the incidence of CBDS was identified. The mean CBD diameter and LFT levels of patients with AC and CBDS were calculated.

Results: Data was extracted from 19 studies representing a total 4057 patients with AC. Routine biliary imaging was not performed in all studies. The pooled incidence of CBDS was 13.7% (95% C.I. 11.8% to 15.9%). The incidence of unsuspected retained CBDS was 1.1%. Histologically confirmed cases of AC had a similar rate of CBDS compared to those diagnosed clinically. The mean CBD diameter of patients with AC and CBDS was 7.2 mm compared to 5.8mm without. LFT values in the presence of CBDS were were more likely to be deranged, with GGT the most sensitive and specific marker for CBDS in the setting of AC.

Conclusion: CBDS is present in a significant proportion of patients presenting with AC. Routine biliary imaging is

advised in all patients presenting with AC where possible.

Introduction:

Common bile duct stones (CBDS) mostly arise as gallstones migrate from the gallbladder into the common bile duct (CBD), and may be symptomatic or asymptomatic. This may be associated with derangements in liver function tests (LFTs) or dilation of the CBD. Biliary imaging available to diagnose CBDS includes ultrasound (US), magnetic resonance cholangiopancreatography (MRCP), computed tomography (CT) with cholangiography, endoscopic retrograde cholangiopancreatography (ERCP), and intraoperative cholangiography (IOC). Although ERCP can be used to diagnose CBDS, it is generally reserved as a therapeutic modality to remove CBDS once diagnosed by another modality. Intraoperative cholangiography during a laparoscopic cholecystectomy may proceed to a laparoscopic common bile duct exploration as a therapeutic modality to remove CBDS.

The incidence of CBDS in patients undergoing elective laparoscopic cholecystectomy (LC) is 10% to 18% [1, 2]. LFTs and CBD diameter when used individually have limited utility in diagnosing CBDS preoperatively, owing to significant false positive and negatives rates[2, 3]. When combined, their diagnostic value improves and allows for more selective use of specific biliary imaging[4, 5]. CBDS presenting without derangement of LFTs and a normal CBD diameter is described as “incidental”, and is found in 3% to 7% of patients undergoing elective LC[6, 7]. While CBDS can cause serious complications such as acute pancreatitis and acute cholangitis, the prognosis of incidental CBDS is poorly understood.

CBDS in the setting of acute cholecystitis (AC) adds further complexity to the understanding of CBDS. AC is believed to be caused by impaction of gallstone at Hartmann’s pouch causing cystic duct obstruction[8, 9]. In this setting passage of stones into the bile duct via the cystic duct may be prevented. On the other hand, the proximity between Hartmann's pouch and the cystic duct might facilitate entry of stones into the CBD. While the incidence of CBDS in patients undergoing elective LC is well researched, there are few studies examining patients undergoing LC for AC. In addition, sepsis due to gallbladder inflammation in the setting of AC can result in LFT derangement, reducing the specificity of LFTs in diagnosing CBDS [10, 11]. The objective of this study is to determine the incidence of CBDS in patients with a diagnosis of AC. To achieve this, a systematic literature search was performed for studies examining incidence of CBDS in patients with AC as well as the value of clinical predictors for CBDS in the setting of AC.

Methods:

Literature search:

A systematic search of the literature using PubMed, Medline and Embase databases up to March 2018 was undertaken. Medical subject headings (MeSH) terms used include “acute cholecystitis”, “choledocholithiasis”, “common bile duct stone” and “common bile duct calculi”. Abstracts of the retrieved studies were screened independently by two reviewers. Relevant studies were identified, and relevant data extracted.

Inclusion and exclusion criteria:

Studies that demonstrated the incidence of CBDS in adult patients diagnosed with AC were included if biliary imaging was performed in at least 50 per cent of the patients in the study. The method of diagnosis of AC, either histologically (with microscopic features, such as edema, hemorrhage and an acute inflammatory infiltrate, consistent with AC as determined by a pathologist) or clinically (by presence of criteria including a local sign, a systemic sign or radiological evidence) was noted in the meta-analysis (see Table 1). Conference papers containing the relevant information were also included. For duplicate articles, the most recently published ones were selected. Studies were excluded if they were not published in English, or if there was no full text available. This review excluded review articles, case reports, letter to the editor and paediatric studies.

Data extraction:

Data was extracted in a standardized manner. This included the incidence of CBDS, the total number of patients with AC and the number of patients receiving specific biliary imaging. Unsuspected CBDS was defined as patients presenting with retained CBDS post LC. Where possible, the mean LFT levels and CBD diameter on US were retrieved.

Statistical analysis:

Due to sizeable heterogeneity across studies, a meta-analysis was performed following the exclusion of outlier studies after combining the studies using a random effects meta-analysis. All meta-analysis-associated calculations were performed using functions from the "meta" library in the R statistical computing environment[12, 13]. A funnel plot was used to explore bias and heterogeneity amongst the studies and to reveal which studies considered to be outliers. Outlier studies were then excluded from analysis and remaining studies were used to produce a forest plot for graphical summarization of findings and determination of pooled incidence of CBDS. Relationships between categorical variables were statistically analyzed using chi-squared or Fisher exact test where appropriate.

Results:

Study selection:

715 studies were identified by the initial search. After applying the inclusion and exclusion criteria, 693 studies were excluded, leaving 22 studies to be included in our analysis[3, 11, 13-31] (Figure 1). Boys et al.[16] included 2588 patients diagnosed with AC of which only 248 (9.6%) had biliary imaging and was not used for assessing cumulative CBDS calculations. A funnel plot was performed and 2 outlier studies were excluded[11, 19] (Figure S1). The remaining 19 studies with a total of 4057 patients with AC were included in this systematic review[3, 14, 15, 17, 18, 20-33] (Figure 2).

Incidence of CBDS in patients diagnosed with AC:

The incidence of CBDS reported range from 3.36% to 25%. A total of 4057 patients diagnosed with AC were involved in 19 studies examined. This includes 557 patients who also have CBDS identified as well as 3500 patients with AC alone. The characteristics of the studies identified are shown in Table 1. Six studies were conducted in Asian countries[14, 20, 27, 31-33], 12 were conducted in Europe or the USA[3, 15, 17, 18, 21, 22, 24-26, 28-30]and 1 was conducted in Israel[23]. The overall incidence of CBDS in patients with AC was estimated as 13.7% (95% C.I. 11.8% to 15.9 %) (Figure 2). 15 studies reported the number of patients receiving specific biliary imaging. Patients received routine biliary imaging in six studies[3, 15, 25, 26, 31, 32] while selective imaging policy was adopted in the remaining 9 studies[17, 18, 20, 21, 23, 24, 27-29]. The incidence of CBDS in those that received routine imaging was 14.7% (95% C.I. 10.9% to 19.7 %) and was not statistically significantly different to those studies that utilised selective imaging 14.2% (95% C.I. 11.1 % to 17.9 %) (p=0.96) (Figure S2).

The criteria used for the diagnosis of AC was reported by 15 studies. AC was diagnosed by histology in 5 studies[15, 17, 18, [21, 29], whereas 8 studies used clinical diagnosis[3, 14, 20, 22, 23, 25, 31, 32]. Two studies employed a combination of histology and clinical diagnosis[24, 26]. The method of AC diagnosis was not reported in six studies[11, 19, 27, 28, 30, 33]. Patients from studies of histologically confirmed AC had similar incidence of CBDS compared with those diagnosed clinically (15.4% vs. 13.4%; p = 0.159).

Unsuspected CBDS:

Follow-up data was reported by four studies with duration of follow-up ranging from 1 to 6 years[17, 21, 24, 33]. Three studies reported on patients presenting with symptoms after LC that were subsequently diagnosed with unsuspected CBDS[21, 24, 33]. All of the 3 studies adopted a policy of selective biliary imaging. The incidence of retained symptomatic CBDS ranged from 0.4% to 1.9%. Out of a total of 860 patients with AC, there were 9 cases of retained symptomatic CBDS representing 1.1% of patients diagnosed with AC.

Clinical predictors:

CBD diameter on ultrasound (US) was only reported by three studies[16, 32, 34]. Their characteristics are demonstrated on Table S1. The mean CBD diameter in patients with AC/CBDS was 7.2 mm while that of patients with AC alone was 5.8 mm. Wong et al.[32] reported a low sensitivity of CBD diameter in diagnosing CBDS (approximately 50%) but without specifying the cut-off point. Meanwhile Boys et al.[16] noted that CBDS occurred at similar rate in those with CBD diameter under 6mm, those between 6 and 9mm as well as those with CBD over 9 mm.

LFT levels in patients with CBDS in AC were reported in 6 studies[14, 17, 24, 28, 30, 34]while those in patients with AC alone were reported by 5[14, 24, 28, 30, 34]. Their characteristics are shown on Table S2. In patients with AC with CBDS, the average

ALT was 268 IU/L; GGT 394 IU/L; ALP 199 IU/L; bilirubin 47 mmol/L and AST 216 IU/L. In patients with AC alone, the average ALT was 79 IU/L; GGT 149 IU/L; ALP 108 IU/L; bilirubin 23 mmol/L and AST level 76 IU/L. Sensitivity and specificity of each parameter was discussed in 4 studies as is shown on Table S3. Kelly et al.[30] demonstrated a tendency for LFT derangement in AC patients without CBDS. Despite this, the severity of derangement is still significantly higher in those with CBDS[14, 24, 34]. GGT appears to be the most reliable predictor for CBDS, although the cut-off point reported by Ahn et al.[14] (GGT 187 IU/L) , Peng et al.[24] (GGT 87 IU/L) and Padda et al. [34] (GGT 74 IU/L) differed appreciably.

Discussion:

CBDS are believed to be present in 10% to 18% of patients undergoing elective LC[1, 2]. There are however only a limited number of studies reporting on the topic of CBDS in the setting of AC, and as far as the authors are aware, this is the first systematic review. The studies published on this topic of CBDS likely reflect differences in the study populations and imaging techniques. We identified 19 studies across 11 countries with data on the incidence of CBDS in patients diagnosed with AC. The incidence of CBDS varied from 2.4% to 25% between individual studies. An important factor accounting for such variation is the difference in the number of patients receiving specific biliary imaging. The majority of studies applied selective biliary imaging[17, 18, 20, 21, 23, 24, 27-29]. Given that selective imaging does not identify the presence of incidental CBDS, this means that selective imaging studies are likely to under-estimate the incidence of CBDS, with many patients remaining asymptomatic following surgery and not having the CBDS discovered. Studies based on patients presenting for elective LC have concluded that up to 4% of CBDS were unsuspected[7, 35]. This may explain the reason for the relatively small number of CBDS reported by studies when a low proportion of patients undergo biliary imaging[16, 18, 23].

It should be noted that the accuracy of the diagnosis of AC may vary depending on whether clinical or histological criteria are utilized. Many studies did not specify the method of diagnosis and most of them relied on a clinical diagnosis without histological confirmation. Patients with chronic cholecystitis (CC) may be mistakenly included in studies of AC if histologic confirmation is not utilized, as visual appearance does not allow definitive diagnosis. The proportion of patients with CC included in those with clinically diagnosed AC is unknown and the extent to which this would have affected the result of the study is therefore uncertain.

There is a paucity of information regarding unsuspected retained CBDS in setting of AC which is diagnosed during the follow-up period after LC. Very few studies included in our systematic review had follow-up data. In those where this was reported, the incidence of retained symptomatic CBDS ranged from 0.4% to 1.9% and appears to be lower than reported by previous studies done on patients undergoing elective LC[6, 7, 35]. A systematic review performed by Metcalfe et al.[35], compiling the result of 9 series of 5179 patients yielded an unsuspected retained CBDS incidence of 4% in patients undergoing LC. The studies examined were not limited to elective or emergency cases or to a diagnosis. With regard to long-term consequences of unsuspected CBDS, Metcalfe et al.[35] concluded that only 15% of patients with unsuspected CBDS (overall 0.6% of patients) develop symptoms. However, the period of follow-up in the studies was limited with only 348 patients from one series followed up for a maximum of 96 months and most patients were followed up for less than 5 years. The mean time of detection of unsuspected CBDS has been reported to vary between 4 years to up to 9.5 years[36-38]. It is estimated spontaneous passage of incidental bile duct stones occurs in 30% to 73% of cases[39, 40]. Studies report that most retained CBDS become symptomatic and about one quarter of patients develop serious complications[37, 41].

CDB diameter and LFT derangement as predictors of CBDS have been examined in several studies. A large systematic review examining the effectiveness of CBD diameter and LFT derangement in predicting CBDS yielded inconclusive results[42]. This review involved studies that were not specific for patients with AC. The CBD diameter is expected to increase with CBDS, but also increases with age [43-46], which may explain differences in CBD diameters between studies with significant age differences. [16, 32] While CBDS is known to be associated with increased CBD diameter, little is known about the degree of CBD dilation in the presence of CBDS and AC. Surprisingly, the mean CBD diameter in patients with AC and CBDS was 7.2 mm in the studies examined, which is close to the upper limit of normal. A more clinically relevant question is the cut-off point at which to prompt the use of specific pre-operative biliary imaging. Previous studies have a CBD diameter cut-off of 10mm has excellent sensitivity for CBDS, but has low specificity[39, 47, 48]. These studies were conducted on patients presenting for LC with a variety of indications and not limited to AC. The profile of CBD diameter in patients with CBDS in the setting of AC is uncertain.

The value of predicting the presence of CBDS in AC based on LFT abnormalities is well described for elective LC. Previous studies that focused on elective LC yielded low sensitivity in CBDS detection even when abnormalities in two or more LFT parameters were combined[3, 49]. Whilst most patients undergoing elective LC without CBDS would have normal LFT levels, it is interesting to note a tendency of derangement in all parameters except for ALP in the presence of AC even without CBDS. This implies a different set of cut-off points needs to be determined in the setting of AC to achieve high sensitivity and specificity. At a similar sensitivity and specificity, the cut-off point for ALT and GGT used by Ahn et al.[14] in their study was almost twice as high as those used by Peng et al.[14, 24, 34] and Padda et al.[14, 24, 34]. Patients selected by Ahn et al.[14] and Peng et al.[14, 24, 34] all had clinically diagnosed AC and possibly included a variable number of patients with CC. In the studies examined, elevations in GGT appear to be the most reliable predictor of CBDS in the setting of AC although the cut-off point reported varied significantly between the different studies[14, 24, 34].

Conclusion:

The incidence of CBDS in AC patients varies widely between 2.4% and 25% with a pooled incidence estimated to be 13.7%. The relatively high incidence of CBDS supports the need for routine biliary imaging in these patients. Intra-operative cholangiogram would be considered a suitable form of routine biliary imaging. Surgical units that manage AC generally have treatment protocols appropriate to their environment and local expertise, which guides how CBDS are managed once discovered.

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Disclosure statement

The Authors have no conflict of Interest' s in relation to this paper

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Supporting Documents

Figure S1

Funnel plot from meta-analysis of 19 studies. Data from the two omitted (large) studies, Song et al., 2014[11] and Grinberg et al., 2015[19]) have been added to this plot and coloured red. A test for asymmetry in the funnel plot (from 19 studies) yielded p = 0.16.

Figure S2.

Forest plot showing the pooled incidence of CBDS in studies that utilized selective 14.2% (95% C.I. 11.1 % to 17.9 %) versus routine biliary imaging 14.7% (95% C.I. 10.9% to 19.7 %), with no statistically significant difference seen between the two screening techniques (p=0.96 chi-square statistic)

Table S1

Mean CBD diameter of patients with AC/CBDS compared with patients with AC alone

Table S2

LFT levels of patients with AC/CBDS compared with LFT levels of patients with AC alone

Table S3

Sensitivity and Specificity of Liver function tests for predicating the presence of CBDS in patients with AC.

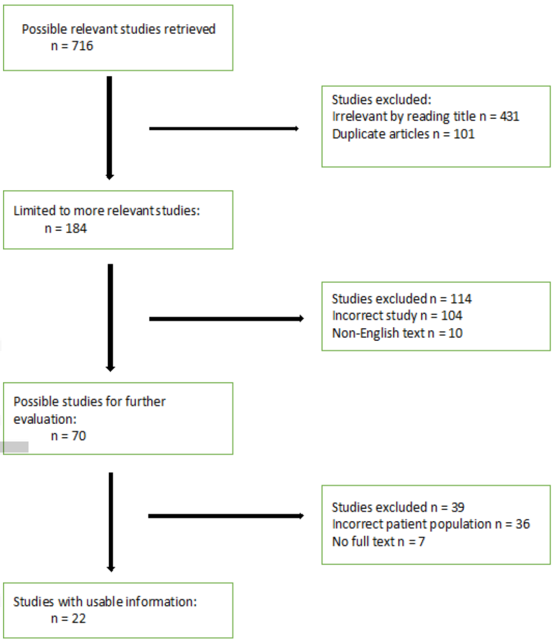
LEGENDS

Figure 1.

Prisma Flow Diagram showing the number of papers retrieved and reviewed to yield the studies for analysis.

Figure 2.

Forest plot from random effects meta-analysis from data from 19 studies on the prevalence of common bile duct stones. The pooled incidence of CBDS was 13.7% (95% C.I. 11.8% to 15.9 %) and the I^2 statistic for heterogeneity was 65.8% (95% C.I. 44.5%; 78.9%).


Possible relevant studies retrieved
n = 716
Studies excluded:
Irrelevant by reading title n = 431
Duplicate articles n = 101
Limited to more relevant studies:
n = 184
Studies excluded n = 114
Incorrect study n = 104
Non-English text n = 10
Possible studies for further evaluation:
n = 70
Studies excluded n = 39
Incorrect patient population n = 36
No full text n = 7
Studies with usable information:
n = 22

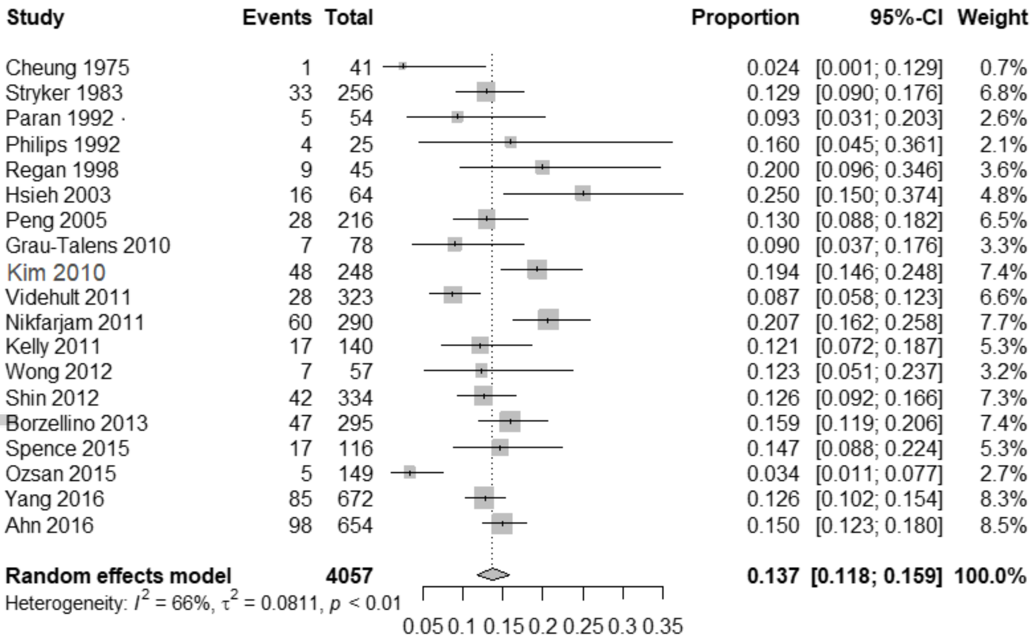
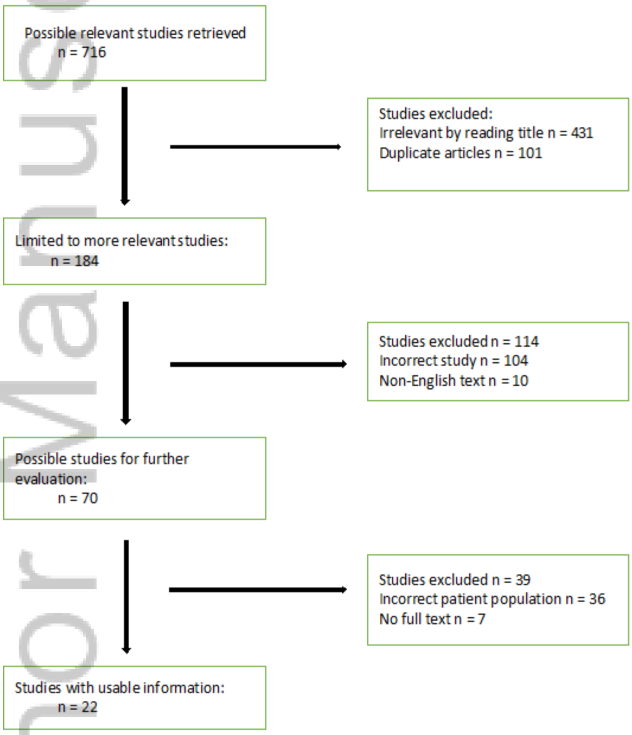

Study Events Total Proportion 95%-CI Weight
Cheung 1975 1 41 0.024 [0.001; 0.129] 0.7%
Stryker 1983 33 256 0.129 [0.090; 0.176] 6.8%
Paran 1992 · 5 54 0.093 [0.031; 0.203] 2.6%
Philips 1992 4 25 0.160 [0.045; 0.361] 2.1%
Regan 1998 9 45 0.200 [0.096; 0.346] 3.6%
Hsieh 2003 16 64 0.250 [0.150; 0.374] 4.8%
Peng 2005 28 216 0.130 [0.088; 0.182] 6.5%
Grau-Talens 2010 7 78 0.090 [0.037; 0.176] 3.3%
Kim 2010 48 248 0.194 [0.146; 0.248] 7.4%
Videhult 2011 28 323 0.087 [0.058; 0.123] 6.6%
Nikfarjam 2011 60 290 0.207 [0.162; 0.258] 7.7%
Kelly 2011 17 140 0.121 [0.072; 0.187] 5.3%
Wong 2012 7 57 0.123 [0.051; 0.237] 3.2%
Shin 2012 42 334 0.126 [0.092; 0.166] 7.3%
Borzellino 2013 47 295 0.159 [0.119; 0.206] 7.4%
Spence 2015 17 116 0.147 [0.088; 0.224] 5.3%
Ozsan 2015 5 149 0.034 [0.011; 0.077] 2.7%
Yang 2016 85 672 0.126 [0.102; 0.154] 8.3%
Ahn 2016 98 654 0.150 [0.123; 0.180] 8.5%
Random effects model 4057 0.137 [0.118; 0.159] 100.0%
Heterogeneity: I^2 = 66%, τ^2 = 0.0811, p < 0.01
0.05 0.1 0.15 0.2 0.25 0.3 0.35

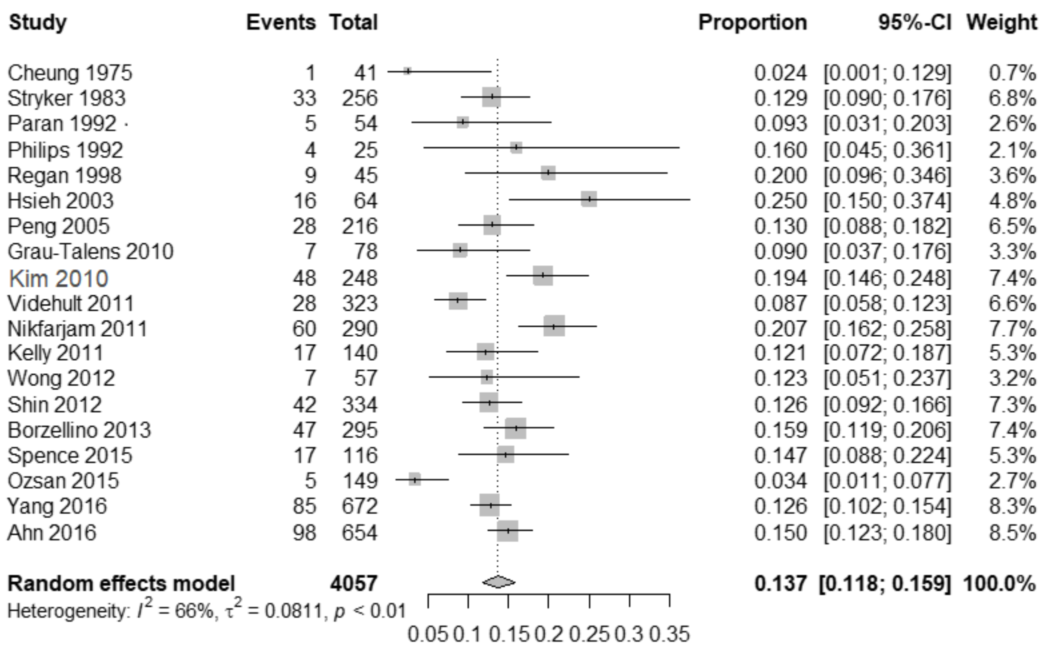
Table 1: Characteristics of included studies

Study ID	Patients with AC	Patients with CBD stones	Incidence of CBD stones in AC patients	Country where study was conducted	How AC is confirmed	Average age
Spence	116	17	14.70%	UK	Unknown	Unknown
Song	1178	246	20.90%	South Korea	Unknown	57.4
Wong	57	7	12.28%	Taiwan	Clinical	55.79
Videhult	323	28	8.67%	Sweden	Clinical	Unknown
Stryker	256	33	12.90%	USA	Histological	54.7
Cheung	41	1	2.40%	USA	Histological	54
Peng	216	28	13%	Britain	Histological /radiological	54
Nikfarjam	290	60	21%	Australia	Histological	61
Borzellino	295	47	15.93%	Italy	Histological	66.1
Regan	45	9	20%	USA	Clinical/histological	Unknown
Grau-Talens	78	7	8.97%	Spain	Histological	62.4
Grinberg	321802	73648	23%	USA	Unknown	Unknown
Hsieh	64	16	25%	Taiwan	Clinical	55.2
Kim	248	48	19.3%	South Korea	Radiological	Unknown
Kelly	140	17	12.10%	Unknown	Unknown	59.3
Oszan	149	5	3.36%	Turkey	Clinical	46.3

Paran	54	5	9.26%	Israel	Clinical	61
Philips	25	4	16%	USA	Clinical	Unknown
Shin	334	42	12.60%	South Korea	Unknown	Unknown
Yang	672	85	12.60%	South Korea	Unknown	Unknown
Ahn	654	98	15%	South Korea	Clinical	58.2



ANS_15565_Figure 1.tif



ANS_15565_Figure 2.tif

Table 1: Characteristics of included studies

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