Bilaga till rapport

Operation vid besvär av sten i gallblåsan och akut gallblåseinflammation
Rapport 259 (2016)

Bilaga 1 Tabeller över beskrivningar av ingående studier

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SBU Statens beredning för medicinsk och social utvärdering • www.sbu.se
Telefon 08-412 32 00 • **Fax** 08-411 32 60 • **Organisationsnummer** 202100-4417
Besöksadress S:t Eriksgatan 117, Stockholm • **Postadress** Box 61836183, 102 3333 Stockholm

Table 14.1 Cholecystectomy versus no cholecystectomy in symptomatic gall stone decease.

Author Year Reference Country	Study period	Cholecystectomy / no cholecystectomy n	Age	Type of study	Exclusions	Op tech	Outcome measures early/late	Conversion	Follow up time	Harms	Over all death	Study quality
Schmidt et al Norway 2011 [16]	Inclusion 1991-1994	68/69	Mean range) 49.7 (20-79) years	RCT uncomplicated gallstone disease Same population as Søndenaa et al 1997 [18] but here is also a third hospital included, i.e. same population as Vetrhus et al 2002 [22].	See Søndenaa et al 1997 [18]	Not described	Conversion rate and rate of adverse gall stone related events	50.5 % randomized to observation underwent operation (median time 28 months). 88.2% randomized to operation underwent operation (median time 3 months). Very few operations performed after 5 years.	Mean (range) 14 (13.5-16) years	1 patient each randomized to observation with acute cholecystitis, common bile duct stone and pancreatitis. In patients randomized to operation 1 had an acute pancreatitis caused by ERCP prior to operation and 4 ERCP were performed with 1 CBD stone detected. P for events 0.3.	Overall 13.9%, non for gall stone disease, equal between groups	Medium
Schmidt et al Norway 2011 [17]	Inclusion 1991-1994	31/33	See Vetrhus et al 2005 [19]	RCT acute cholecystits. See Vetrhus M "quality of…" 2003. Same population but longer follow-up.	See Vetrhus et al 2005 [19]	Laparoscopic/ open/ converted(n) in cholecystectomy group 45/15/0 And in observation	See Vetrhus et al 2005 [19]	87.1% in cholecystectomy group and 33.3% in observation group had undergone surgery	Mean (range) 14 (13-16) years.	10/33 patients in observation group experienced complicated gall stone disease (cholecystitis, CBD, and/or gallstone pain, the latter being n=1).	8/10 deaths, none caused by gallstone disease or gallbladder cancer.	Medium

Author Year Reference Country	Study period	Cholecystectomy / no cholecystectomy n	Age	Type of study	Exclusions	Op tech	Outcome measures early/late	Conversion	Follow up time	Harms	Over all death	Study quality
						group 29/2/4				6 /31 patients in the operation group experienced complicated gall stone disease (pain attacks n=4).		
Søndenaa et al Norway 1997 [18]	Inclusion 1991-1994	Symptomatic gall bladder stone 59/61 Symptomatic gall bladder stone and cholecystitis 31/33	Median (range) 51 (20-79) and 57 (26-77) respectively	RCT 4 hospitals recruited but only 2 had substantial patient recruitment and only these 2 were thus included	Age < 18 or > 80, pregnancy, gangrenous gallbladder, suspected CBD stone, achalculos cholecystitis, patient preferred symptoms (6.8%), severer or well tolerable symptoms.	Not described	Conversion rate	12% of patients with no chole-cystitis and 13% with a history of cholecystitis randomized to operation switched to observation. Corresponding figures for patients randomized to observation switching to operation were 25 and 24% respectively.	1.5-4 years, mean not given.	Not described	Not described	Medium

Author Year Reference Country	Study period	Cholecystectomy / no cholecystectomy n	Age	Type of study	Exclusions	Op tech	Outcome measures early/late	Conversion	Follow up time	Harms	Over all death	Study quality
Vetrhus et al Norway 2005 [19]	See Søndenaa et al 1997 [18]	31/33	See Søndenaa et al 1997 [18]	See Søndenaa et al 1997 [18]	See Søndenaa et al 1997 [18]	Not described	Pain and QoL at 6, 12 and 60 months. No difference between groups.	See Søndenaa et al 1997 [18]	Median 67 months	N.A.	See Søndenaa et al 1997 [18]	Medium
Vetrhus et al Norway 2003 [21]	Inclusion 1991-1994	31/33	See Søndenaa et al 1997 [18]	See Schmidt et al 2011 [16]	See Søndenaa et al 1997 [18]	Not described	Cumulative risk of cholecystectomy and gall stone related complication.	13 % randomized to operation switched to observation and 30% randomized to operation switched to operation.	Median (range) 67 (56-98) months	Cholecystectomy group/observation group: events (n) Admission for pain 3/4. Acute cholecystitis 1/9. CBD stone 1/4. Acute pancreatitis 1/0. (p=0.09). Patients (n) with any of above mentioned events 6/12 (p=0.16).	See Søndenaa et al 1997 [18]	Medium

Author Year Reference Country	Study period	Cholecystectomy / no cholecystectomy n	Age	Type of study	Exclusions	Op tech	Outcome measures early/late	Conversion	Follow up time	Harms	Over all death	Study quality
See Vetrhus et al 2002 [22]	Inclusion 1991-1994	68/69	See Schmidt et al 2011 [16]	RCT Same population as Schmidt M "a randomized) but shorter follow-up I.e. the same population as Søndenaa et al 1997 [18] but here is also a third hospital included.	See Schmidt et al 2011 [16]	Laparoscopic/ open/ converted(n) in cholecystectomy group 45/15/0 And in observation group 29/2/4	See Schmidt et al 2011 [16] Same outcome measures but with a shorter follow-up.	88 % randomized to operation and 51% randomized to observation underwent operation.	Median (range) 67 (56-91) months.	Major complications (i.e. intra - abdominal infection, bile leakage, wound infection, dehiscence) (n) 3 in cholecystectomy, 5 in observation group.	0/0 related to cholecystectomy or gall bladder stone. No data for total mortality.	Medium
Vetrhus et al Norway 2004 [20]	See Vetrhus et al 2002 [22]	68/69	See Vetrhus et al 2002 [22]	See Vetrhus et al 2002 [22]	See Vetrhus et al 2002 [22]	Laparoscopic/ open/ converted(n) in cholecystectomy group 45/15/0 And in observation group 29/2/4	Pain and QoL at 6, 12 and 60 months. No difference seen over time between groups. Patient with high initial pain randomized to observation were more likely to undergo operation.	See Vetrhus et al 2002 [22]	See Vetrhus et al 2002 [22]	N.A.	See Vetrhus et al 2002 [22]	Medium

Table 14.2 a: Early vs delayed surgery for acute cholecystectomy – systematic reviews and RTCs.

Author Year Country Reference	Study period	n early/ late	Mean age (years) early/late	Type of study	Exclusion	Def early/ late	Op tech	Outcome measures early/late	Conversion early/late	Follow up time	Harms	Over all death	Study quality
Cao et al 2015 [24]		795/813	47	Systematic review 15 RTCs 1998-2014	-	Early with 24 to 96 hours	Not given	Total hospital stay (days mean) 4.1/7.3 p>0.001 Days off work 14.75/23.50 p<0.07			Total complications RR 0.66 (95% CI, 0.42; 1.03) Bile duct leak RR 0.79 (95% CI, 0.27; 2.34) Postoperative wound infection RR 0.57 ()%% CI, 0.35; 0.93) Mortality RR 1.03 (95% CI, 0.05; 20.50)		Medium partly same studies as Gunsuramy 2013 Includes Gutt 2013 and Gul 2013
Studies included in Cao et al. (above)													
Gurusamy et al 2013 * [23]	search until July 2012	244/244	40- 60 years in different studies	Systematic review (6 studies)			Various	Operating time (minutes) MD -1.22 (95% CI -3.07; 0.64) (6 trials) Total hospital stay (days) MD -4.12 (95% CI -5.22; -3.03) (4 trials)	19.7/22.1% RR 0.89; (95% CI 0.63; 1.25) (6 trials).		Complications total 6.5/5.0 % RR 1.29; (95% CI 0.61;2.72) (5 trials) Bile duct injuries 0.4/0.9% OR 0.49; (95% CI 0.05	0/0	Medium/ high Return to work based on 36 patients in one trial

Author Year Country Reference	Study period	n early/ late	Mean age (years) early/late	Type of study	Exclusion	Def early/ late	Op tech	Outcome measures early/late	Conversion early/late	Follow up time	Harms	Over all death	Study quality
								Return to work (days) MD -11,.0 95% CI -19.6; -2.4) (1 trial)			to 4.72) (5 trials)		
Gul et al * 2013 India [26]	2008-2011	30/30	40 (SD 8)/ 38 (SD 10)	RCT 1 hospital	Jaundice, choledocho-lithiasis, pancreatitis, malignancy, previous upper abdominal surgery	<72 hours/ 6-12 weeks	Laparoscopic	Op time (min) 99/81 p<0.05 Blood loss 173/101 (ml) p<0.05 Hospital stay 4.8/10.1 (days) sign	3/4 ns	not given	Fever 2/1 Pneumonia 2/1 Bile leakage 1/0 Intraabdominal collect 0/1 Wound infection 1/1 All ns	not given	Medium/ high
Gutt et al * 2013* Germany/ Slovenia [25]	2006-2010	304/314	56 (SD16)/ 57 (SD17)	RCT Individual 35 centres	ASA 4-5 Septic chock Peroration Abscess Pregnancy	<24 hours after hospital admission n/ 7-45 days	Laparoscopic	Morbidity within 75 days 11.8/34.4% Hospital stay 5.4/10.0 p<0.01 Total hospital costs € 2 919/4 262 p<0.01 Post op hospitalisation 4.7/4.9 p=0.57 Morbidity score on day 75 0.53/1.12 p<0.001	30/33 p= 0.44	75 days	All adverse events 58 (n= 43) / 179 (n=127) Serious adverse events n= 28/85	1/1 ns	High

Table 14.2 b: Early vs delayed surgery for acute cholecystectomy – Retrospective comparative register study.

Author Year Country Reference	Study period	n early/ late	Mean age (years) early/late	Type of study	Exclusion	Def early/ late	Op tech	Outcome measures early/late	Conversion early/late	Follow up time	Harms	Over all death	Study quality
de Mestral et al 2014 Canada [27]	2004-2011	14 948/ 7 254	53 (SD18)/ 56 (SD 17)	Retrospec-tive compara-tive register study 154 hospitals in Ontario	Severe cholecystitis, Biliary malignancy	≤7days/ median 8 weeks (IQR 4-12 weeks)	Laparoscopic 21 280 Open 922	Post op hospital stay (days) hospital stay MD -1.9 (95% CI -2.1: -1.7)	1 220/719	>6 months	Major bile duct injury n = 38/39 0.28%/0.53 % RR 0.53 (95% CI 0.31; 0.90)	at 30 days 0.46%/ 0.64% RR=0.73, (95% KI: 0.47; 1.15)	Medium

Table 14.3: Laparoscopic vs open cholecystectomy for cholecystitis.

Author Year Country	Study period	Number and gender laparoscopic/ open	Median age (years) laparoscopic/open	Randomisation	Indication for surgery	Assessment and follow-up	Results laparoscopic/ open	Harms: Complications/ Mortality laparoscopic/ open	Surgery time (min) laparoscopic/ open	Study quality
Coccolini et al 2015 Italy and Ireland [32]	1989-2010	n = 677/697 Gender not stated.	Not given	Systematic review meta-analysis 4 RCT and 6 observational (4 retropective and 2 prospective)			Postoperative length of stay (1 RCT, 1 observational MD -4.74 (95% CI, -9.05; -0.43)	LC vs OC Complications 4 RCTs LC 27/154 OC 43/156 OR 0.54 (95% CI, 0.31; 0.94) 4 RCT + 5 observational studies OR 0.46 (95% CI, 0.34, 0.61) Bile leakage 1 RCT, 3 observational studies OR 1,26 (95% CI, 0.34; 4.62) Mortality 4 observational studies OR 0.20 (95% CI, 0.04; 0.89)	MD -90 (95% CI, -18.11; 16.31)	Medium. Not entirely consequent reporting of the different parameters. Errors in numbering of tables Includes all the above RTCs

Author Year Country	Study period	Number and gender laparoscopic/ open	Median age (years) laparoscopic/open	Randomisa-tion	Indica-tion for surgery	Assess-ment and follow-up	Results laparoscopic/ open	Harms: Complications/ Mortality laparoscopic/ open	Surgery time (min) laparoscopic/ open	Study quality
Studies included in Coccolini et al (above)										
Boo et al 2007 Korea [28]	May-2004 to December 2004	n = 33 18/15 9 women 9 men/ 9 women 6 men	LC 53±16 OC 63±13 (P=0.062)	RCT (Computer randomiztion)	Acute cholecystitis	Preoperati veday 1, day 3 postoperative.	a/ "LC causes less surgical trauma and immunosuppression than OC". b/ Hospital stay (days) 3.7±1.2/6.3±2.7	Complications LC 0/15 OC 2/18 no significant difference no mortality	73.2±24/ 90.2±23 ns	Medium+
Catena et al 2013 Italy/ [29]	2 years	n = 164 20 not included, 11 refused, 9 requested LC 72 72 Gender not given	>18 Median not given	RCT (Randomized computer to envelopes)	Acute cholecystitis Early (<72 hours)	Preoperative Peroperative Discharge, 7days 1 month 6 months	Conversion rate LC 9.7% (7/72) "Outcome of LC not different from OC in AC". Length of stay in hospital (days) 5.1/5.4	Complications: OC 25/72 LC 24/72 (ns) 1 bile leakage from the cystic duct in LC group. no mortality	109/98 ns	Medium/Low poor data description ? Randomization. Process 2/3 gangrene or empyema.
Johansson et al.2005 Sweden [30]	Apr 2002-Mar 2004	35/35 (16 women, 19 men/ 19 women, 16 men)	53 (23-84)/ 56 (31-80) ns	RCT (Double blind. Sealed envelopes stratified for age and sex Individually)	Acute cholecystitis Symptoms >6hr + lab.	Preoperative during hospital stay and postop (4 w)	Conversion: 8/35 Sick leave ns Pain score at discharge ns	Complications LC 2/35 OC 3/35 ns no bile leakage	90 (30-155)/ 80 (50-170) (P=0.04)	Medium , Questions regarding statistics. Biased?

Author Year Country	Study period	Number and gender laparoscopic/ open	Median age (years) laparoscopic/open	Randomisa-tion	Indica-tion for surgery	Assess-ment and follow-up	Results laparoscopic/ open	Harms: Complications/ Mortality laparoscopic/ open	Surgery time (min) laparoscopic/ open	Study quality
					Not more than 6 days.	Pain score at discharge, Sick Leave,	Length of stay in hospital (days) 2 (1-10)/2 (1-8) p=0.011	No mortality		High conversion rate.
Kiviluoto et al 1998 Finland [31]	Jan 95-Aug 96	n = 32/31 Gender not stated.	61.4 (28-82)/58.9 (25-88)	RCT (Blinded, Sealed envelopes.)	Acute cholecystitis Consecutive >24 hours pain + lab	1-2 months	Length of stay in hospital LC 4 (2-5) OC 6 (5-8) (p=0.006) Sick leave (days) 13.9/30.9 (p=<.0001) Postoperative complications Major 0/32/7/31(p=0.0048) Minor 1/32/6/31 (p=0.0530)	Complications LC 1/32 OC 13/31 No mortality.	108.2 (±49.9)/ 99.8 (±39.7) ns	High

MD = mean difference; OR = odds ratio; RTC = randomized controlled trial

Table 14.4: Laparoscopic and open cholecystectomy for cholecystitis – harms, observational studies.

Author Year Country	Study period	n and Gender	Median age (years) (range)	Study design	Aim	Indication for surgery	Assessment and Follow-up	Bile duct injuries	Other complications	Mortality	Study quality
Adamsen et al 1997 Denmark [35]	1991-1994	n=7 654 Gender not stated.	Not stated	Register study. All laparoscopic cholecystectomies 1991-1994	Assess bile duct injury after LC incidence, types treatment	Symptomatic gallstone and complications Elective and acute laparoscopic cholecystectomy.	Preoperative Peroperative 30 days follow-up.	57 (0.74%) 84% occurred before conversion to OC. Incidence BDI was not reduced during the study period. 2.1% of LC had bile leakage without BDI.		18% in those with bile duct injury	Medium- Lacking coverage rate and overall mortality.
Pessaux et al 2001 France [37]	January 1992-December 1999	n=139 LC n=50 OC n=89 LC 30 women 20 men. OC 51 women, 38 men	>75	Observational Prospective inclusion of patients >75 with acute cholecystitis	Determine the feasibility and the efficacy of LC for AC in patients >75year and compare with OC.	Acute cholecystitis	All preoperative, and postoperative data were collected prospectively on standardized forms.	None	Postoperative complications, wound infection, subhepatic collection, retained CBD stones, cardiogenic pulmonary oedema, arrhythmia, renal failure, urinary infection would haematoma, septic shock	4/139 (all after OC)	Medium Selection bias? Long waiting times.

Author Year Country	Study period	n and Gender	Median age (years) (range)	Study design	Aim	Indication for surgery	Assessment and Follow-up	Bile duct injuries	Other complications	Mortality	Study quality
									taken together. LC 9/50 (18%) OC 19/89 (21.3%)		
Strömberg et al 2015 Sweden [36]	2006-2011	n=62 488 41 859 women 20 628 men	<50 29 676; 50-70 25 139 >70 7 671 Data missing 2	All cholecystectomies 2006-2011. Register study Cross-matched with National patient register.	Report the incidence of and risk factors for symptomatic venous thromboembolism after cholecystectomy.	All cholecystectomies.	Peroperative Postoperative 30 day follow-up.	-	Venous thromboembolism in 154 (0.25%). Deep venous thrombosis in 36 (0.06%) Pulmonary embolus in 25 (0.04%). Standardized incidence rate for deep venous thrombosis 22.2 (95% CI, 13.1; 31.3) Standardized incidence rate for pulmonary embolus 5.6 (95% CI, 2.3; 8.9)	Not stated	High

Author Year Country	Study period	n and Gender	Median age (years) (range)	Study design	Aim	Indication for surgery	Assessment and Follow-up	Bile duct injuries	Other complications	Mortality	Study quality
Harboe et al 2011 Denmark, [34]	January 2006-June 2009	20 307 patients 73% women	49 (4-101)	Register study	Assess the quality of LC and OC in Denmark	Gallstone and complications	Conversion rate Length of hospital stay Additional procedures Readmission 30 day mortality	0,2 % BDI 5,6 % additional . procedures LC and OC together	Conversion rate LC 7.6% Reconstructive	54/ 20 307 (0.27%)	Medium. Does not differ LC and OC completely
Törnqvist et al [33] 2015 Sweden	2005-2010	51 041 67 % women	51 (38-63) in those without BDI	Register study (GallRiks)	All BDI	All, 18.2 % cholecystitis	Register (GallRiks)	747 (1.5%)		no mortality	High
Rystedt et al [9] 2016 Sweden	2007-2011	55 134 60 % women	62 (3-99)	Register study (GallRiks)	Severe BDI (Hannover scale C or higher	All, 43.7 % uncomplicated gallstone disease	Patient records in those registered with BDI	174 (0.3%)		6/55 134 (0.01%)	High

BD = bile duct; BDI = bile duct injury; GallRiks = national quality register for cholecystectomies and ERCP; LC = 0 laparoscopic cholecystectomy; OC = open cholecystectomy

Table 14.5: Economic evaluations comparing surgery (cholecystectomy) with observation/conservative management.

Author **Year** **Reference** **Country**	**Study design** **Population** **Setting** **Perspective**	**Intervention** **vs** **control**	**Incremental cost**	**Incremental effect**	**ICER**	**Study quality and transferability*** **Further information** **Comments**
Brazzelli et al [41] 2014 UK	Model-based CUA Time horizon 5 years Population from 2 RCTs on adults with first episode of symptomatic uncomplicated gallstone disease, suitable for cholecystectomy Secondary care NICE Health and Personal Social Services perspective	Base case model estimates for female aged 51 years I: Surgery C: Conservative management (surgery if symptoms persist)	All costs reported in GBP year 2011/2012 I: 2 340 C: 1 104 Difference: 1 236	Effects reported in QALYs I: 4.232 C: 4.139 Difference: 0.094	13 205 per QALY Conservative management most probable cost-effective at a willingness to pay per QALY below 20 000	High study quality High transferability to Sweden Further information in [16,17] Results very sensitive to probability of surgery and to QoL of patients with persistent symptoms in conservative management
de Mestral et al [42] 2016 Canada	Model-based CUA Time horizon 5 years Register data. Adults with acute cholecystit without previous symptomatic gallstone disease, admitted to ED March 2004-April 2011 (25 545 patients). Propensity score matched Hospital Third party payer perspective (Ontario Ministry of Health and Long Term Care)	Three arms: 1: Early surgery (within 7 days of symptoms) 2: Delayed surgery 3: Watchful waiting (urgent surgery if recurrent symptoms)	All costs reported in CAD year 2011 1: 6 905 3: 7 275 Difference: 370	Effects reported in QALYs 1: 4.20 3: 3.99 Difference: -0.21	Watchful waiting dominated by Early surgery (less cost and more QALYs) Sensitivity analyses (threshold and probabilistic) confirm dominance of Early surgery	High study quality High transferability to Sweden Further information in [11,27] Results sensitive to QoL post surgery See table 14.6 for the second arm results
Sandzén et al [10] 2013 Sweden	Register-based descriptive study Swedish National Patient Register data. Patients with gallbladder disease (no previous admission for biliary diagnosis for 2 years) admitted to hospital	Four patient groups: 1: Surgery at admission 2: Elective surgery within 2 years	No costs reported Resource consumption reported as mean days of hospital stay, including index admission	Not reported	Not reported	Study quality assessed as observational study; medium risk of bias 41 % of patients found in group 4. No surgery within 2 years

	January 1988-December 2006 (302 043 admissions) Hospital No costs reported	3: Emergency surgery within 2 years 4. No surgery (cholecystectomy) within 2 years	and 2-year admissions for biliary diagnoses 1: 7.57 2: 8.55 3: 12.98 4: 8.05 Difference: 4 vs 1: 0.48 days			See table 14.6 for the second patient group results

* Study quality is a combined assessment of the quality of the study from a clinical as well as an economic perspective

CUA = Cost-utility analysis; GBP = British pound; QoL = quality-of-life; ED = emergency department; CAD = Canadian dollars

Table 14.6: Economic evaluations comparing early acute surgery (cholecystectomy) with delayed elective surgery (cholecystectomy).

Author **Year** **Reference** **Country**	**Study design** **Population** **Setting** **Perspective**	**Intervention vs control**	**Incremental cost**	**Incremental effect**	**ICER**	**Study quality and transferability*** **Further information** **Comments**
Gutt et al [25] 2013 Germany and Slovenia	RCT-based CA Follow-up 75 days Adult patients with symptoms of acute cholecystitis and possibility of laparascopic surgery within 24 hours of admission 618 patients from 35 centres Hospital Hospital perspective	I: Immediate surgery, mean day of surgery 0.6 days C: Conservative treatment and delayed elective surgery, mean day of surgery 25.1 days	All costs reported in EUR year 2010 I: 2 919 C: 4 262 Mean total hospital days: I: 5.4 (95 % CI: 5.08 – 5.71) C: 10.03 (95 % CI: 9.36 – 10.69)	-	-	Moderate study quality Moderate transferability to Sweden 75-day morbidity score statistically significant lower in Immediate group
Johansson et al [43] 2003 Sweden	RCT-based, resource consumption Patients aged <91 years with diagnosis acute cholecystitis 145 patients Hospital No costs reported	I: Laparoscopic surgery within 7 days of symptom onset C: Conservative treatment and delayed elective surgery 6-8 weeks later	Total hospital days, median: I: 5 C: 8	-	-	Moderate study quality Moderate transferability to Sweden 26 % of patients in Delayed group required emergency surgery
Wilson et al [45] 2010 UK	Model-based CUA Time horizon 1 year Patients with acute cholecystitis. Many event probabilities from Gurusamy et al, 2010 [51] Hospital	I: Early surgery C: Delayed surgery	All costs reported in GBP year 2006 Per 1000 patients: I: 2 574 457 C: 3 395 997	Effects reported in QALYs Per 1000 patients: I: 876.48 C: 825.05	Delayed surgery dominated by Early surgery (less cost and more QALYs) Early surgery has a 70 % probability of being cost-effective against Delayed at a willingness	High study quality High transferability to Sweden Patient groups not clearly described

	NICE healthcare perspective		Difference: −821 540	Difference: 51.43	to pay 20 000 per QALY, and decreased to a 62 % probability at a willingness to pay 30 000	
Johner et al [44] 2013 Canada	Model-based CUA Time horizon 1 year Patients with acute cholecystitis. Most event probabilities from Gurusamy et al, 2010 [51] Hospital Healthcare perspective	I: Early surgery C: Delayed elective surgery as defined in [51]	All costs reported in CAD year 2009 I: 5 408.50 C: 7 538.26 Difference: -2 129.76	Effects reported in QALYs I: 0.9733 C:0.9434 Difference: 0.0299	Delayed surgery dominated by Early surgery (less cost and more QALYs)	Moderate study quality Moderate transferability to Sweden Few sensitivity analyses reported
de Mestral et al [42] 2016 Canada	Model-based CUA Time horizon 5 years Register data. Adults without previous symptomatic gallstone disease, admitted to ED March 2004-April 2011 (25 545 patients) Propensity score matched. Hospital Third party payer perspective (Ontario Ministry of Health and Long Term Care)	Three arms: 1: Early surgery (within 7 days of symptoms) 2: Delayed surgery (elective 8-12 weeks later) 3: Watchful waiting	All costs reported in CAD year 2011 1: 6 905 2: 8 511 Difference: 1 606	Effects reported in QALYs 1: 4.20 2: 4.18 Difference: -0.02	Delayed surgery dominated by Early surgery (less cost and more QALYs) Sensitivity analyses (threshold and probabilistic) confirm dominance of Early surgery	High study quality High transferability to Sweden Further information in [11,27] See table 14.5 for the third arm results
Sandzén et al [10] 2013 Sweden	Register-based descriptive study Swedish National Patient Register data. Patients with gallbladder disease (no previous admission for biliary diagnosis for 2 years) admitted to hospital January 1988-December 2006 (302 043 admissions)	Four patient groups: 1: Surgery at admission 2: Elective surgery within 2 years	No costs reported Resource consumption reported as mean days of hospital stay, including index admission and 2-year	Not reported	Not reported	Study quality assessed as observational study; medium risk of bias See table 14.5 for the fourth patient group results

	Hospital No costs reported	3: Emergency surgery within 2 years 4. No surgery (cholecystectomy) within 2 years	admissions for biliary diagnoss 1: 7.57 2: 8.55 3: 12.98 4: 8.05 Difference: 2 vs 1: 0.98 days			

* Study quality is a combined assessment of the quality of the study from a clinical as well as an economic perspective

CA = Cost analysis; EUR = Euros; CI = confidence interval; CUA = Cost-utility analysis; CAD = Canadian dollars; GBP = British pounds; ED = emergency department