Multi-society State-of-the-Art Consensus Conference on Prevention of Bile Duct Injury During Cholecystectomy

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State of the Art Consensus Conference on Prevention of Bile Duct Injury During Cholecystectomy

Saturday, October 20, 2018 • Boston, MA

PICO 8

Timing of Cholecystectomy in Acute Cholecystitis

PICO 8 Team (and PICO 11)

Waala Abelmoaty
Maria Altieri
Blaire Anderson
Saxon Conor
Chet Hammill
Scott Dolejs
Steven Strasberg
Megan Thomas

PICO 8 Question

Should immediate cholecystectomy (within 72 hrs from symptom onset) vs CCX delayed beyond 72 hours (< 6 weeks vs >6-12 weeks) be used for acute cholecystitis?

Introduction

- Important Background Studies
- Types of Timing Studies Available
- Results of GRADE Analysis
- Type A Recommendations
- Type B Recommendations

Background: (Tornqvist et al World J Surg (2016) 40:1060)

Severity of Acute Cholecystitis and Risk of Iatrogenic Bile Duct Injury During Cholecystectomy, a Population-Based Case–Control Study

Björn Törnqvist[1] · Anne Waage[2] · Zongli Zheng[3] · Weimin Ye[3] · Magnus Nilsson[1]

- A very important study on the relationship between severity of AC and occurrence of BDI
- From clinical records and not an administrative database
- Adjusted risk of bile duct injury was doubled among patients with acute cholecystitis (OR 1.97 95 % CI 1.05–3.72).

Background: (Tornqvist et al World J Surg (2016) 40:1060–1067)

Severity of Acute Cholecystitis and Risk of Iatrogenic Bile Duct Injury During Cholecystectomy, a Population-Based Case–Control Study

Björn Törnqvist[1] · Anne Waage[2] · Zongli Zheng[3] · Weimin Ye[3] · Magnus Nilsson[1]

- Mild acute cholecystitis (Tokyo grade I) did not affect the risk of BDI
- Moderate (Tokyo grade II) **more than doubled** the risk (OR 2.41 95 % CI 1.21–4.80).

Prior attacks of AC also significantly increased the odds ratio for BDI (OR 3.63 95 % CI 2.00–6.57)

Severity Grading of Acute Cholecystitis

Failure to consider severity grade may result in:

1.Imbalance in terms of severity grade with more mild or moderate severity in one group i.e., imbalance in likelihood of having BDI occur.

2.Inclusion of one grade over another – ie the severity grade in two groups might be equal but equally imbalanced toward mild acute cholecystitis with misleadingly low BDI rate. Not representative samples

How Many Timing Studies Included Severity Grading of AC?

How Many Timing Studies Included Severity Grading of AC?

PICO 8 Recommendation

Later we will vote on a recommendation regarding the need to grade severity of AC and history of prior attacks of AC in studies of AC and BDI

Background 2: Incorrect Diagnosis of AC

In patients with gallstones who come to the ED with right upper quadrant pain there may be a bias to declaring that the diagnosis is AC vs biliary colic.

This is because diagnosis affects leveling and leveling affects access to resources and perhaps payment for provider services. Generally this is thought to be innocent since the patients have an indication for cholecystectomy.

Background 2: Incorrect Diagnosis of AC

If the admission and discharge diagnosis by the surgeon is “acute cholecystitis” and the pathology report has the word “cholecystitis” albeit “chronic cholecystitis” there is a danger that the ICD code selected by a coder will be acute cholecystitis even though there is no acute cholecystitis.

If such patients are entered in a timing trial the early group will contain some patients that do not even have acute cholecystitis and this will bias results in favor of early cholecystectomy.

Diagnosis of Acute Cholecystitis by Validated Methods

- Tokyo Guidelines
  - 1 Local sign
  - 1 General sign
  - Radiologic confirmation
- Histological examination

Questionable Diagnosis of AC in Published Studies

- Of 13 evaluable randomized controlled trials 10 fulfilled TG criteria of 1 local sign 1 systemic signs and a radiographic confirming sign.

- Of 45 evaluable observational studies 22 or just less than half fulfilled TG criteria.

PICO 8 Recommendation

Later we will vote on a recommendation regarding acceptable criteria for the diagnosis of acute cholecystitis in clinical studies

Background : Inflammation in AC and Timing of Cholecystectomy

- There is a controversy regarding the timing of cholecystectomy in acute cholecystitis.

- That controversy relates to the sequence of inflammatory changes that occur after onset of symptoms.

Background : Inflammation in AC and Timing of Cholecystectomy

- In classical theory after onset of symptoms of AC there is an early period in which inflammatory conditions are favorable for cholecystectomy, an intermediate period in which conditions are less favorable, and a late period in which they become more favorable again.
- Often the early period is subdivided into two periods.
- In studies there is a large variation in what is considered to be early and what is considered to be late.
- For consistency among studies a framework regarding these time periods would be helpful.

Cao et al 2015 7/14 studies chose within 72 hr as “early” and 10/14 studies chose > 6wks as late

Table 1 Study demographics

Study	Country	Time	Patients randomised (*n*)	Number of patients (*n*)—early/late	Jadad score	Definition of early (<h)	Definition of late (>weeks)
Lai 1998	Hong Kong	Jan 1993 to Dec 1995	104	53:51	3	24	6–8
Lo 1998	Hong Kong	Nov 1994 to Dec 1996	99	49:50	2	72	8–12
Davila 1999	Spain	Feb 1995 to Apr 1998	63	27:36	2	96	8
Chandler 2000	United Sates	Jun 1996 to Jun 1998	43	21:22	2	72	5 days
Johansson 2003	Sweden	Dec 1998 to Dec 2000	145	74:71	2	48	6–8
Kolla 2004	India	Jan 2001 to Nov 2002	40	20:20	3	24	6–12
Ghani 2005	Pakistan	Jun 1997 to Jun 1998	102	50:52	1	Immediate surgery	Interval surgery
Yadav 2009	Nepal	Feb 2003 to Jun 2004	50	25:25	2	As soon as possible	6–8
Mare 2012	Switzerland	Feb 2009 to Mar 2012[a]	54	27:27	2	72	6
Faizi 2013	Pakistan	Jan 2010 to Dec 2011	50	25:25	2	72	Possibly 5 weeks (unclear)
Gul 2013	India	Jul 2008 to Jul 2011	60	30:30	2	72	6–12
Gutt 2013	Germany and Slovenia	2006 to Nov 2010	618	304:314	3	24	1–7
Verma 2013	India	Aug 2010 to Mar 2012	60	30:30	3	72	6–8
Saber 2014	Egypt	Apr 2009 to Nov 2014	120	60:60	3	72	6–8
Total			1608	795:813			Mean age

Gutt CN, et. Acute cholecystitis: early versus delayed cholecystectomy, a multicenter randomized trial. Ann Surg 2013; 258(3):385-93.

- 1 of 15 papers in the MA of Cao et al
- 620 of 1608 (39%) in the MA of Cao et al
- Early = <24hr
- Late = >1 week

Proposed classification of interval between time of onset of symptoms and time of operation in acute cholecystitis for use in clinical studies

Phase 1. Onset of symptoms to 72 hours. Inflammation expected to be favorable for cholecystectomy - tissue swelling due to edema.

Phase 2. 72 hrs to 10 days. Inflammation expected to be less favorable for cholecystectomy. Tissue swelling and increased vascularity

Phase 3. 10 days to 6 weeks. Inflammation expected to be much less favorable for cholecystectomy – Acute and chronic inflammation.

Phase 4. 6 weeks or later. Inflammation expected to be more favorable again for cholecystectomy. Predominately chronic inflammation

PICO 8 Recommendation

Later we will vote on a recommendation regarding the proposed classification of time of onset of symptoms and time of operation in acute cholecystitis that should be used as a framework to guide future studies.

Types of Timing Studies

- About 80 observational trials
- About 18 RCTs
- About 8 metaanalyses of RCTs
- One systematic review of the metaanalyses

J Gastrointest Surg (2015) 19:848–857
DOI 10.1007/s11605-015-2747-x

ORIGINAL ARTICLE

Early Cholecystectomy Is Superior to Delayed Cholecystectomy for Acute Cholecystitis: a Meta-analysis

Amy M. Cao · Guy D. Eslick · Michael R. Cox

Comparative Operative Outcomes of Early and Delayed Cholecystectomy for Acute Cholecystitis

A Population-Based Propensity Score Analysis

Charles de Mestral, MD, PhD,‡ Ori D. Rotstein, MD, MSc,† Andreas Laupacis, MD, MSc,†‡ Jeffrey S. Hoch, MA, PhD,†‡ Brandon Zagorski, MS,‡ Aziz S. Alali, MD,* and Avery B. Nathens, MD, PhD, MPH*†‡*

Song et al. Medicine (2016) 95:23

Table 2

Primary RCTs incorporated into each eligible meta-analysis.

Primary RCTs	Meta-analyses included						
	Papi et al 2004[15]	Siddiqu et al 2008[16]	Gurusamy et al, 2013[14]	Zhou et al, 2014[12]	Cao et al, 2015[13]	Menahem et al, 2015[2]	Wu et al, 2015[3]
Lai, 1998[24]	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Lo, 1998[25]	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Dávila, 1999[26]			Yes	Yes	Yes		Yes
Chandler, 2000[27]	Yes				Yes		
Khan, 2002[28]							Yes
Johansson, 2003[29]		Yes	Yes	Yes	Yes	Yes	Yes
Johansson, 2004[30]							Yes
Kolla, 2004[31]		Yes	Yes	Yes	Yes	Yes	
Ghani, 2005[32]					Yes		
Yadav, 2009[33]				Yes	Yes	Yes	Yes
Macafee, 2009[34]						Yes	Yes
Mare, 2012[35]					Yes		Yes
Faizi, 2013[36]					Yes		Yes
Gul, 2013[37]					Yes	Yes	Yes
Verma, 2013[38]					Yes		Yes
Gutt, 2013[39]				Yes	Yes	Yes	Yes
Saber, 2014[40]					Yes		Yes
Ozkardes, 2014[41]						Yes	Yes

RCT, randomized controlled trial.

Song et al. Medicine (2016) 95:23

Table 5

AMSTAR criteria for each included study.

Items	Papi et al (2004)[15]	Siddiqu et al (2008)[16]	Gurusamy et al, (2013)[14]	Zhou et al (2014)[12]	Cao et al (2015)[13]	Menahem et al (2015)[2]	Wu et al (2015)[3]
Was a prior design provided?	0	1	1	0	0	0	0
Was there duplicate study selection and data extraction?	1	1	1	1	1	1	1
Was a comprehensive literature search performed?	1	1	1	1	1	1	1
Was the status of publication (i.e., Gray literature) used as an inclusion criterion?	0	1	1	1	0	0	1
Was a list of studies (included and excluded) provided?	0	0	1	0	0	0	0
Were the characteristics of the included studies provided?	1	1	1	1	1	1	1
Was the scientific quality of the included studies assessed and documented?	1	1	1	1	1	1	1
Was the scientific quality of the included studies used appropriately in formulating conclusions?	1	1	1	1	1	1	1
Were the methods used to combine the findings of studies appropriate?	1	1	1	1	1	1	1
Was the likelihood of publication bias assessed?	1	1	1	1	1	1	1
Was the conflict of interest stated?	1	1	1	1	1	1	1
Total scores	8	10	11	9	8	8	9

DeMestral et al - Ann Surg 2014

- A population-based retrospective cohort study of patients emergently admitted to hospital with acute cholecystitis and managed with cholecystectomy divided into 2 exposure groups
- Those who underwent cholecystectomy within 7 days of emergency department presentation on index admission (early cholecystectomy) and those whose cholecystectomy was delayed average of 8 weeks.
- Primary outcome was major bile duct injury requiring operative repair within 6 months of cholecystectomy.
- Propensity score methods were used to address confounding by indication.
- Early cholecystectomy was associated with a lower risk of major bile duct injury [0.28% vs 0.53%, relative risk (RR)=0.53, 95% confidence interval: 0.31-0.90.

DeMestral et al - Ann Surg 2014

- The diagnosis of acute cholecystitis was derived by medical record abstractors who confirm the diagnosis contained in the discharge summary with medical imaging and pathology reports.
- Because clinical markers of severity (eg fever, white blood cell count) and the details of imaging and pathology reports were not contained in our data sets, differentiating mild from moderate cholecystitis was not possible.

Dx by ICD code.

Severity not accounted for

Should

IMMEDIATE CHOLECYSTECTOMY

(WITHIN 72 HOURS From SYMPTOM ONSET)

versus

CHOLECYSTECTOMY DELAYED BEYOND 72 HOURS

(BUT < 10 days AFTER SYMPTOM ONSET)

versus

CHOLECYSTECTOMY DELAYED BEYOND 6 WEEKS

versus

CHOLECYSTECTOMY DELAYED BEYOND 12 WEEKS

be used for patients with acute cholecystitis?

GRADE Results for Bile Duct Injury

Absolute Effect	
With Delayed Cholecystectomy	**With** Immediate Cholecystectomy
5 per 1000	3 per 1000

Difference: 2 fewer per 1000 patients

(95% CI: 1 to 4 fewer per 1000 patients)

Based on data from 14220 patients in 1 study

RR 0.53

(0.31 to 0.9)

Differences in outcomes

Favours Immediate Cholecystectomy	Favours Delayed Cholecystectomy

2 fewer per 1000 patients

⊕OOO

VERY LOW

Due to serious risk of bias.
Due to serious indirectness.
Due to serious imprecision.

GRADE Results for Mortality

Absolute Effect

With Delayed Cholecystectomy	With Immediate Cholecystectomy
2 per 1000	2 per 1000

Difference: 0 fewer per 1000 patients

(95% CI: 1 fewer to 30 more per 1000 patients)

Based on data from 1293 patients in 8 studies

RR 1.03

(0.05 to 20.5)

Differences in outcomes

Favours Immediate Cholecystectomy	Favours Delayed Cholecystectomy

0 fewer per 1000 patients

⊕OOO

VERY LOW

Due to serious risk of bias.
Due to serious indirectness.
Due to very serious imprecision.

GRADE Results for Conversion

Absolute Effect	
With Delayed Cholecystectomy	**With** Immediate Cholecystectomy
154 per 1000	132 per 1000

Difference: 22 fewer per 1000 patients
(95% CI: 54 fewer to 20 more per 1000 patients)
Based on data from 1452 patients in 12 studies

RR 0.86
(0.65 to 1.13)

Differences in outcomes

Favours Immediate Cholecystectomy	**Favours** Delayed Cholecystectomy

22 fewer per 1000 patients

⊕OOO
VERY LOW

Due to serious risk of bias.
Due to serious indirectness.
Due to very serious imprecision.

GRADE Results for Patients with Complications

Absolute Effect	
With Delayed Cholecystectomy	**With** Immediate Cholecystectomy
299 per 1000	197 per 1000

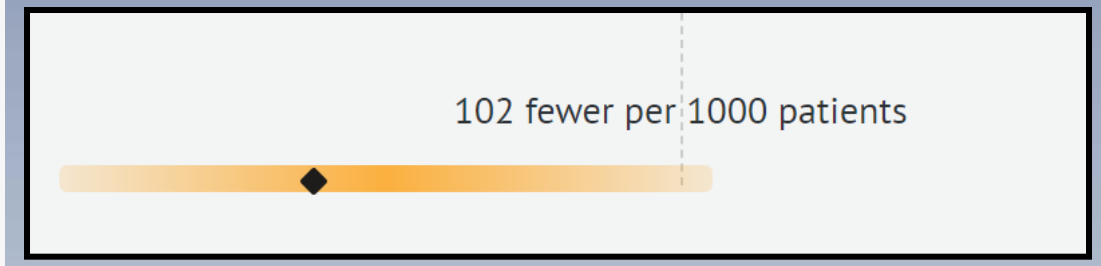
Difference: 102 fewer per 1000 patients

(95% CI: 173 fewer to 9 more per 1000 patients)

Based on data from 1268 patients in 9 studies

Differences in outcomes

Favours Immediate Cholecystectomy | **Favours** Delayed Cholecystectomy



RR 0.66

(0.42 to 1.03)

⊕OOO

VERY LOW

Due to serious risk of bias.
Due to serious inconsistency.
Due to serious indirectness.
Due to very serious imprecision.

GRADE Results for Wound Infection

Absolute Effect

With Delayed Cholecystectomy	With Immediate Cholecystectomy
62 per 1000	35 per 1000

Difference: 27 fewer per 1000 patients
(95% CI: 4 to 41 fewer per 1000 patients)
Based on data from 1145 patients in 8 studies

RR 0.57
(0.35 to 0.93)

Differences in outcomes

Favours Immediate Cholecystectomy	Favours Delayed Cholecystectomy

27 fewer per 1000 patients

⊕OOO
VERY LOW

Due to serious risk of bias.
Due to serious indirectness.
Due to very serious imprecision.

GRADE Results for Total Hospitalization

Absolute Effect		Certainty of the evidence
With Delayed Cholecystectomy	With Immediate Cholecystectomy	GRADE
7.3 days	4.1 days	⨁◯◯◯ VERY LOW
Average difference (MD): 3.2 days fewer (95% CI: 1.3 to 5.1 fewer days) Based on data from 1383 patients in 11 studies		Due to serious risk of bias. Due to serious indirectness. Due to very serious imprecision.

GRADE Results for Duration of Surgery

Absolute Effect		Certainty of the evidence GRADE
With Delayed Cholecystectomy	With Immediate Cholecystectomy	
86 min	99 min	⨁◯◯◯ VERY LOW

Average difference (MD): 13 min more
(95% CI: 8.13 fewer to 34.12 more min)
Based on data from 1276 patients in 10 studies

Due to serious risk of bias.
Due to serious indirectness.
Due to very serious imprecision.

GRADE Summary of Judgements

CRITERIA	SUMMARY OF JUDGEMENTS				
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large	
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**	
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High	
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability	
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes	
FEASIBILITY	No	Probably no	Probably yes	**Yes**	

Summary of PICO 8 Grade Results

- Certainty: Very Low

- No difference between early and late cholecystectomy in:
  - Mortality
  - Patients with complication
  - Conversion to open cholecystectomy

Summary of PICO 8 Grade Results

- Favors early cholecystectomy:
  - Length of hospital stay
  - Wound infections
- Favors late cholecystectomy:
  - Duration of surgery
- Indeterminate
  - Bile Duct Injury

Indeterminate - Bile Duct Injury

- In MILD acute cholecystitis early versus late lap chole is unlikely to be an issue in BDI because overall rate of BDI is not increased over that in patients without acute cholecystitis
- However in MODERATE acute cholecystitis the overall rate of BDI is doubled. Therefore baseline equality in Tokyo Guideline Severity Grading is needed in studies of timing of operation in acute cholecystitis.
- Thus far no adequately powered timing study with the outcome measure BDI has taken severity grade into account.

PICO 8 Recommendations from GRADE Results (Type A)

- In patients presenting with mild acute cholecystitis (according to Tokyo Guidelines), we suggest surgeons perform laparoscopic cholecystectomy within 72 hours of symptom onset (conditional recommendation, very low certainty of evidence)

- For patients with moderate and severe cholecystitis there is insufficient evidence to make a recommendation, particularly as it relates to the outcome of bile duct injury.

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Other Notable Studies

Early laparoscopic cholecystectomy is superior to delayed acute cholecystitis: a meta-analysis of case–control studies

Amy M. Cao[1] · Guy D. Eslick[1] · Michael R. Cox[1]

Surg Endosc (2016) 30:1172–1182

Early Versus Delayed Cholecystectomy for Acute Cholecystitis, Are the 72 hours Still the Rule?

A Randomized Trial

Didier Roulin, MD, Alend Saadi, MD, Luca Di Mare, MD, Nicolas Demartines, MD, FACS, FRACS, and Nermin Halkic, MD

(*Ann Surg* 2016;264:717–722)

Optimal treatment strategy for acute cholecystitis based on predictive factors: Japan-Taiwan multicenter cohort study

J Hepatobiliary Pancreat Sci (2017) 24:346–361

Itaru Endo · Tadahiro Takada · Tsann-Long Hwang · Kohei Akazawa · Rintaro Mori · Fumihiko Miura · Masamichi Yokoe · Takao Itoi · Harumi Gomi · Miin-Fu Chen · Yi-Yin Jan · Chen-Guo Ker · Hsiu-Po Wang · Seiki Kiriyama · Keita Wada · Hiroki Yamaue · Masaru Miyazaki · Masakazu Yamamoto

- PICO 8 Recommendations from GRADE Results (Type B)

PICO 8 Recommendation 8. B1

Recommendation regarding the need to grade severity of AC and history of prior attacks of AC in studies of AC and BDI

PICO 8 Recommendations Type B
B1 Regarding the need to grade severity of AC and history of prior attacks of AC

Studies that examine the relationship between bile duct injury and acute cholecystitis should match patients at baseline both for severity grade of acute cholecystitis and history of prior attacks of acute cholecystitis. This recommendation is based on the finding that the incidence of major bile duct injury is significantly higher in moderate grade acute cholecystitis than in mild grade acute cholecystitis and the finding that the incidence of bile duct injury is higher in patients who have had prior attacks of acute cholecystitis than those who have not.

Vote on PICO 8 B1 Recommendation

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PICO 8 Recommendation 8.B2

Recommendation regarding acceptable criteria for the diagnosis of acute cholecystitis in clinical studies

PICO 8 Recommendations Type B
B2 : Diagnosis of AC

The diagnosis of acute cholecystitis should be documented in future studies following well accepted clinical criteria such as TG18 diagnostic criteria **or** histologic findings of acute inflammation **or both**. If documentation of acute cholecystitis is based on diagnostic codes such as ICD codes, investigators should ensure that the diagnostic codes were based on the preceding criteria.

Vote on PICO 8 B2 Recommendation

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PICO 8 Recommendation 8.B3

Recommendation regarding the proposed classification of time of onset of symptoms and time of operation in acute cholecystitis that should be used as a framework to guide future studies

PICO 8 Recommendations Type B3 Regarding classification of timing of surgery in studies of acute cholecystitis

In acute cholecystitis for the purposes of reporting standardization and ability to compare results among studies, we suggest that the interval between onset of symptoms and time of operation should be defined in 4 phases (P1-4): P1: Symptom onset to 72 hrs; P2: 72 hours to 10 days; P3: 10 days to 6 weeks; P4: > 6 weeks.

We also recommend that studies define the onset of AC from the onset of patient symptoms rather than from the arrival of the patient to the hospital.

Vote on PICO 8 B3 Recommendation

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PICO 11

Interval Cholecystectomy

versus

No Additional Treatment
in patients previously treated by cholecystostomy

Circumstances Indicating Cholecystostomy over Cholecystectomy at time of Presentation with Acute Cholecystitis

- Type 1. Comorbidities and/or frailty (too chronically ill/too frail)
- Type 2. Acute organ system failure (too acutely sick)
- Type 3. Late presentation
- Type 4. Resources for cholecystectomy unavailable

Types of Patients who are Treated by Cholecystostomy

Patients who receive cholecystostomy	Interval Cholecystectomy?
• Type 1: too chronically ill/too frail	• Probably very few will be fit enough
• Type 2: too acutely sick	• Some or many might be fit enough
• Type 3: late presentation	• Should be eligible for cholecystectomy
• Type 4. resources unavailable	• Should be eligible when resources are available

What would a good comparative study look like?

- From all patients who got cholecystostomy tubes eliminate those who are not fit for interval cholecystectomy and randomize the remainder to interval cholecystectomy or no interval cholecystectomy

What would a good comparative study look like?

- From all patients who got cholecystostomy tubes eliminate those who are not fit for interval cholecystectomy and randomize the remainder to interval cholecystectomy or no interval cholecystectomy

- OR perhaps propensity match to eliminate patients not fit for cholecystectomy

What do the available studies compare?

- All the patients who did not undergo interval cholecystectomy (including the too sick/ too old patients)

versus

- All the patients who did undergo interval cholecystectomy.

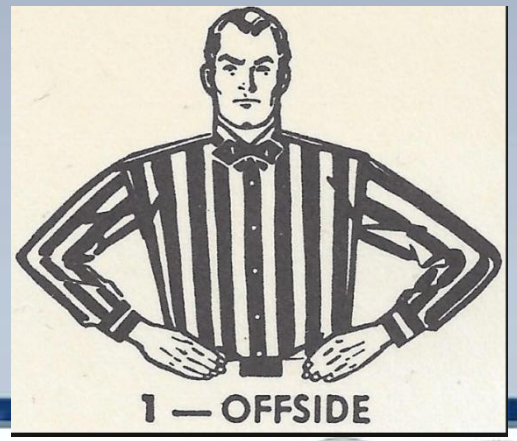
What do the available studies compare?

- All the patients who did not undergo interval cholecystectomy (including the too sick/ too old patients)

versus

- All the patients who did undergo interval cholecystectomy.

- i.e. Unequal at baseline fault



What do the available studies show?

- Limited number of observational studies
- None have the power to draw conclusions regarding Bile Duct Injury

- Notable papers
  - de Mestral (2012) – 890 patients
  - Alvino (2017) – 288 patients
  - Jang (2012) – 93 patients
  - McKay (2012) – 68 patients

Patients who do NOT have elective cholecystectomy

- A sizeable proportion (50-80%) had no further problems after removal of tube.

- Remainder had additional symptoms and some required urgent cholecystectomy often done open – suggesting increased difficulty of surgery in this group (?? Surrogate for Increased risk of BDI)

Patients who have elective cholecystectomy

- These patients are less likely to require urgent cholecystectomy
- These patients are more likely to have cholecystectomy completed laparoscopically.

- So…….

PICO 11 Recommendations from GRADE Results (Type A)

In low risk surgical candidates with acute calculous cholecystitis previously treated by percutaneous cholecystostomy, we suggest interval cholecystectomy after the inflammation has subsided. For **high risk*** candidates, we suggest a non-surgical approach that may include percutaneous stone clearance through the tube tract or tube removal and observation if the cystic duct is patent. (conditional recommendations, very low certainty of evidence).

Comment Regarding “High Risk”

For patients who have had a cholecystostomy tube placed and are being evaluated for elective cholecystectomy (after the acute inflammation has subsided), “high risk” is defined as substantially increased risk of mortality or morbidity associated with elective total cholecystectomy based on multidisciplinary evaluation of the patients health status including comorbidities and frailty.

The evaluation should involve surgeons, anesthesiologists and when deemed advisable other specialists depending on the patients specific health problems. The use of established risk scoring systems may be employed in reaching decisions in this setting.

PICO 11 Recommendations from GRADE Results (Type A)

In low risk surgical candidates with acute calculous cholecystitis previously treated by percutaneous cholecystostomy, we suggest interval cholecystectomy after the inflammation has subsided. For **high risk*** candidates, we suggest a non-surgical approach that may include percutaneous stone clearance through the tube tract or tube removal and observation if the cystic duct is patent. (conditional recommendations, very low certainty of evidence).

Vote on PICO 11 Recommendation

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PICO 11

Interval Cholecystectomy

versus

No Additional Treatment
in patients previously treated by cholecystostomy

Laparoscopic cholecystectomy versus percutaneous catheter drainage for acute cholecystitis in high risk patients (CHOCOLATE)

Multicentre randomised clinical trial

C Loozen, H van Santvoort, P van Duijvendijk, M Besselink, D Gouma, G Nieuwenhuijzen, J Kelder, S Donkervoort, A van Geloven, P Kruyt, D Roos, A Pronk, D van der Peet, R Crolla, K kortram, V Kornmann, B van Ramshorst, T Bollen, D Boerma

Study design

Objective	To assess whether laparoscopic cholecystectomy is superior to percutaneous catheter drainage in high risk patients with acute calculous cholecystitis
Design	Multicentre, randomised controlled, superiority trial
Setting	11 hospitals in the Netherlands, February 2011 to January 2016

Inclusion and exclusion criteria

Inclusion *	Age > 18 Acute calculous cholecystitis Apache-II score ≥ 7
Exclusion	APACHE-II score ≥ 15 Symptoms that lasted > 7 days Pregnancy Decompensated liver cirrhosis ICU admission at the time of diagnosis Mental illness

* Adults with acute calculous cholecystitis and a high surgical risk were included. Risk assessment was based on the APACHE II score. High risk was defined as an APACHE II score of ≥ 7.

Randomisation

Laparoscopic cholecystectomy	Performed < 24 hours Four trocar technique Experienced laparoscopic surgeon
Percutaenous drainage	Performed < 24 hours Transhepatic or transperitoneal route Qualified radiologists Drain left in place for 3 weeks

Outcome measures

Primary	Death	< 1 year
	Major complications	
	Intra-abdominal abscess	
	Pneumonia	
	Myocardial infarction	< 1 month
	Pulmonary embolism	
	Need for re-intervention	< 1 year
	Recurrent biliary disease	< 1 year

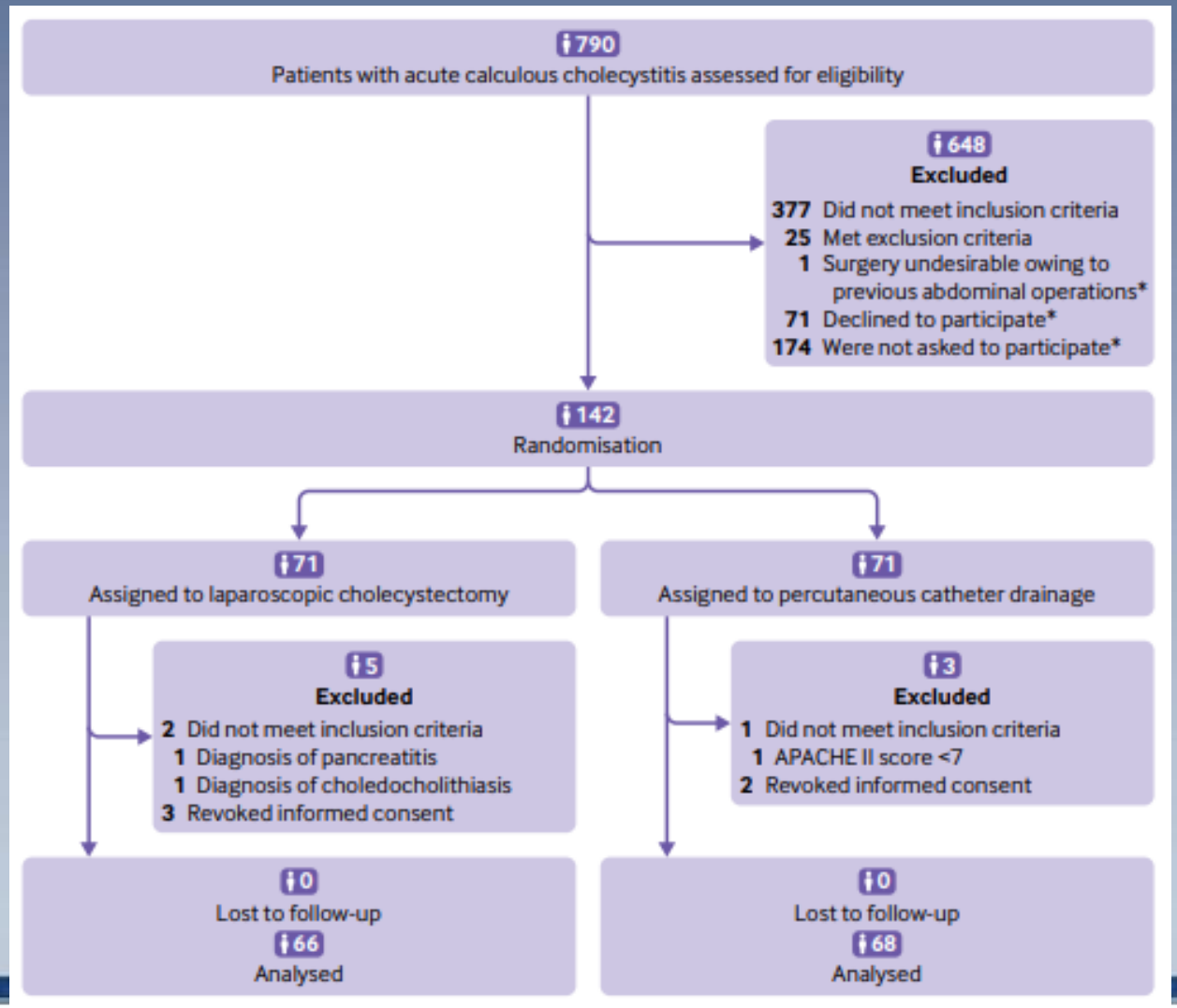
Secondary

Individual components of primary endpoint
Minor complications
Difficulty of cholecystectomy
Utilisation of healthcare resources
Total costs

Statistical analysis

Sample size	284 patients [80% power, 2-sided α 5%, loss-to follow-up 1%]
Interim analysis	50% of patients included Adjudication committee
Premature termination	26 February 2016 (n = 142)

Enrollment, randomisation and follow-up



Baseline characteristics

Characteristics	Laparoscopic cholecystectomy (n=66)	Percutaneous catheter drainage (n=68)
Mean (SD) age (years) **AGE**	71.4 (10.6) **71**	74.9 (8.6) **75**
Men	41 (62)	44 (65)
Mean (SD) body mass index*	28.7 (5.3)	29.0 (5.5)
Coexisting conditions:		
Cardiovascular disease **CV disease**	38 (58) **58%**	53 (78) **78%**
Pulmonary disease	13 (20)	14 (21)
Chronic renal insufficiency	3 (5)	5 (7)
Diabetes	13 (20)	16 (24)
Previous abdominal surgery	16 (24)	10 (15)
ERCP before randomisation	3 (5)	4 (6)
ASA classification on admission:		
I: healthy status	10 (15)	4 (6)
II: mild systemic disease	33 (50)	37 (54)
III: severe systemic disease	23 (35)	24 (35)
IV: severe systemic disease that is a constant threat to life	0	3 (4)
Disease severity:		
Mean (SD) APACHE II score†	9.5 (1.9)	9.4 (2.0)
Mean (SD) C reactive protein level (mg/L)	218.5 (117.2)	214.7 (123.8)
Mean (SD) white blood cell count ($\times 10^9$/L)‡	17.0 (5.1)	17.2 (5.2)
Mean (SD) body temperature (°C)§	37.7 (1.1)	37.8 (0.9)
Median (interquartile range) time since onset of symptoms (days)¶	3 (2 to 3)	2 (1 to 4)

Primary endpoints

	LC (n=66)	PD (n=68)	p value
Death	2 (3%)	6 (9%)	0.27
Major complications	8 (12%)	44 (65%)	<0.001

Secondary endpoints

	Lap Chole	Tube	Risk Ratio	p
Secondary endpoints				
Death, No. (%)	2 (3%)	6 (9%)	0.34 (0.07 to 1.64)	0.27
Infectious and cardio-pulmonary complication, No. (%)	5 (8%)	3 (4%)	0.97 (0.89 to 1.05)	0.49
Need for reintervention, No. (%)	8 (12%)	45 (66%)	0.18 (0.09 to 0.36)	<0.001
Surgical intervention	3 (5%)	32 (47%)	0.10 (0.03 to 0.30)	<0.001
Endoscopic intervention	6 (9%)	11 (16%)	0.56 (0.22 to 1.43)	0.22
Radiological intervention	4 (6%)	15 (22%)	0.28 (0.10 to 0.79)	0.008
Recurrent biliary disease, No. (%)	3 (5%)	36 (53%)	0.09 (0.03 to 0.27)	<0.001
Minor complication, No. (%)	0	4 (6%)		0.12
Health care utilization				
Total length of hospital stay, days, median (IQR)	5 (4 to 8)	9 (6 to 19)		<0.001
Total no. of ER visits per study group (range per pt)	7 (0 to 1)	56 (0 to 5)		<0.001
Total no. of reinterventions per study group (range per pt)	21 (0 to 6)	64 (0 to 4)		<0.001
Total no. of readmissions per study group (range per pt)	9 (0 to 2)	67 (0 to 5)		<0.001
Direct medical costs per patient	$6125	$9110		

Conclusion

Among high risk patients with acute cholecystitis, laparoscopic cholecystectomy compared with percutaneous drainage is the preferred treatment strategy from both a clinical and economical point of view.

Conclusion*

- it should be emphasized that the results of this trial only apply to patients with an APACHE II score of 7 or more and 14 or less, and so do not apply to patients with a score of 15 or more.
- During the study period, however, we only excluded 10 patients on the basis of this criterion.
- This implies that virtually all patients with acute calculous cholecystitis can safely undergo early laparoscopic cholecystectomy.

Multi-society State-of-the-Art Consensus Conference on Prevention of Bile Duct Injury During Cholecystectomy

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Work Group Five

- PICO #10, 12-14

- **Group Leads**
  - Rajesh Aggarwal, MD PhD FACS FRCS, Thomas Jefferson University
  - Carol-Anne Moulton, MBBS PhD FRACS, University of Toronto
- **Group Members**
  - Philip Pucher, MD PhD MRCS, Imperial College London
  - Sara Monafred, MD, University of Indiana
  - Nathan Stoikes, MD, University of Tennessee Health Science Centre
  - Byron Fernando-Santos, MD, Dartmouth-Hitchcock Medical Center
  - Ryan Campagna, MD, Northwestern University
  - Romeo Ignacio, MD, Naval Medical Center San Diego

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PICO #10

- **PICO 10:** Should standard 4-port cholecystectomy versus reduced port laparoscopic cholecystectomy (SILS etc) versus robotic cholecystectomy versus other technique be used for limiting the risk or severity of bile duct injury in candidates for cholecystectomy?
- Primary Outcome – BDI
- Secondary Outcome – Operating Time, Morbidity, Conversion

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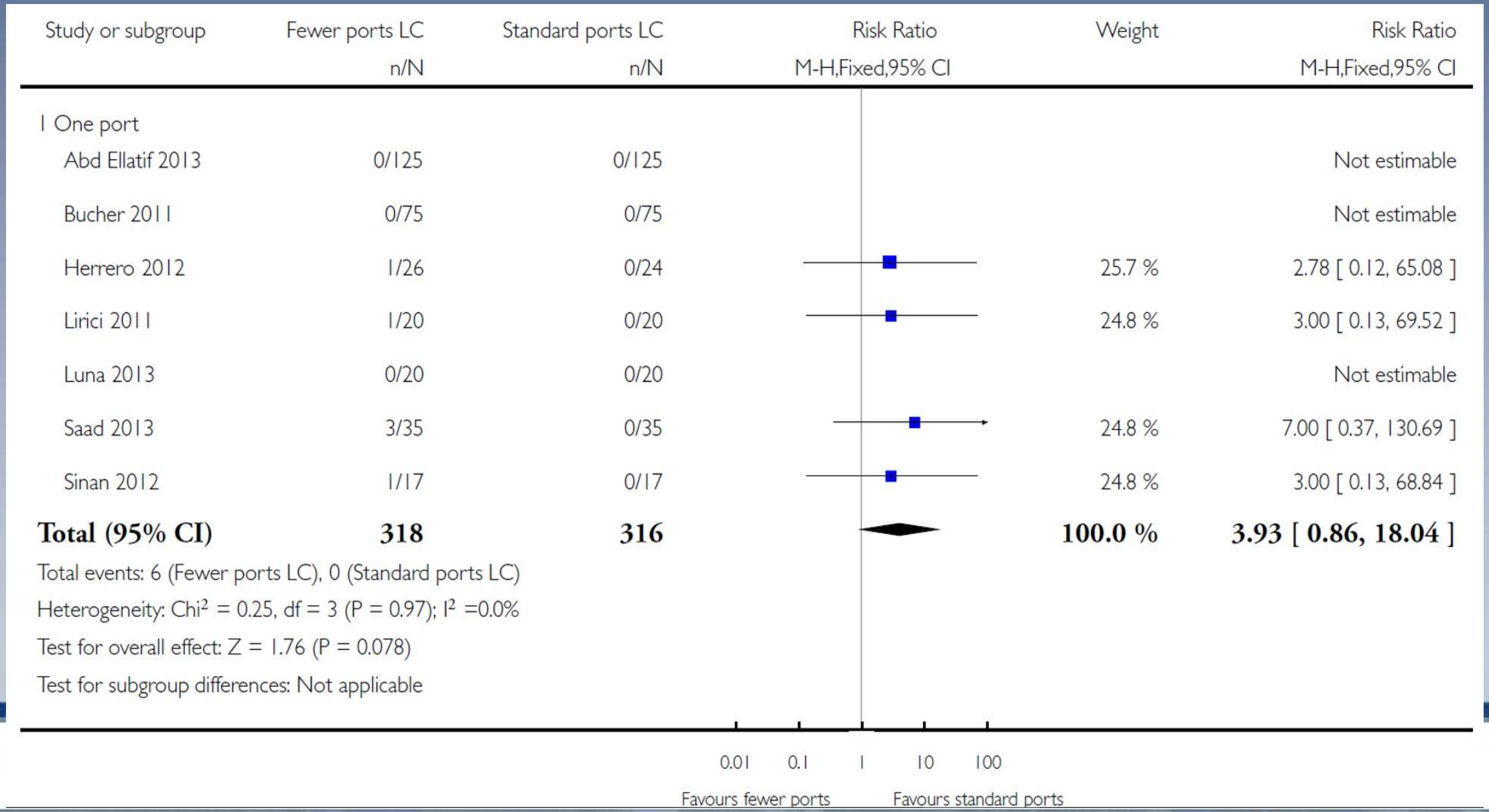
PICO #10


24 studies identified from original search
10 shortlisted for full-text analysis
3 best-evidence studies included in final data synthesis

PICO #10

Outcome	Evidence
Primary outcome	
BDI	A 2014 Cochrane review[1] of 9 RCTs of 4-port vs. reduced port LC (7 trials: single port, 2 trials: 3-port) reported no significant difference in rates of serious adverse events (major complications which included BDI) (RR 3.93 (0.86 – 18.04) 7 trials, n=634, very low quality evidence with high bias risk). A 2012 systematic review of BDI in SILS[2] (45 cohort studies, n=2626), authors reported a higher rate of BDI with SILS (0.72%) from their pooled data than has been previously reported for standard 4-port LC.
Secondary outcomes	
Operating time	The Cochrane review[1] reported a significantly higher mean operating time for SILS vs. 4-port LC (MD 21.04 min; 95% CI 10.45 – 31.62). There was no difference between 3-port and 4-port groups (MD -5.32 min; -17.38 – 6.73).
Morbidity	One RCT (2011, single centre Swiss study)[3] of SILS vs. 4-port LC (n=150) both met the inclusion criteria for this review (assessment of BDI) and reported morbidity; this study found no differences in post-operative morbidity (16% 4-port LC vs. 13% SILS).
Conversion	The 2014 Cochrane review[1] reported no difference in conversion rates for 4-reduced port vs. 4-port LC (RR 0.68 (0.19 – 2.35), 5 trials, n=531, very low quality evidence with high bias risk). There was no difference for subgroup analysis of SILS and 3-port vs. 4-port (numbers not reported).

Fewer-than-four ports versus four ports for laparoscopic cholecystectomy: serious adverse events, CDSR 2014



PICO #10: Recommendation

- Recommendation A: For patients requiring cholecystectomy, we suggest using a multi-port laparoscopic technique instead of single port/single incision technique (conditional recommendation, very low certainty of evidence).

References

1. Gurusamy KS, Vaughan J, Rossi M, Davidson BR. Fewer-than-four ports versus four ports for laparoscopic cholecystectomy. Cochrane Database Syst Rev. 2014 Feb 20;(2):CD007109.

2. Joseph M, Phillips MR, Farrell TM, Rupp CC. Single incision laparoscopic cholecystectomy is associated with a higher bile duct injury rate: a review and a word of caution. Ann Surg. 2012 Jul;256(1):1-6.

3. Bucher P, Pugin F, Buchs NC, Ostermann S, Morel P. Randomized clinical trial of laparoendoscopic single-site versus conventional laparoscopic cholecystectomy. Br J Surg. 2011 Dec;98(12):1695-702.

Vote on PICO 10 Recommendation

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PICO #12

- **PICO 12:** Should conversion of laparoscopic cholecystectomy to open cholecystectomy versus no conversion be used for limiting the risk of bile duct injury during difficult laparoscopic cholecystectomy?
- No relevant data

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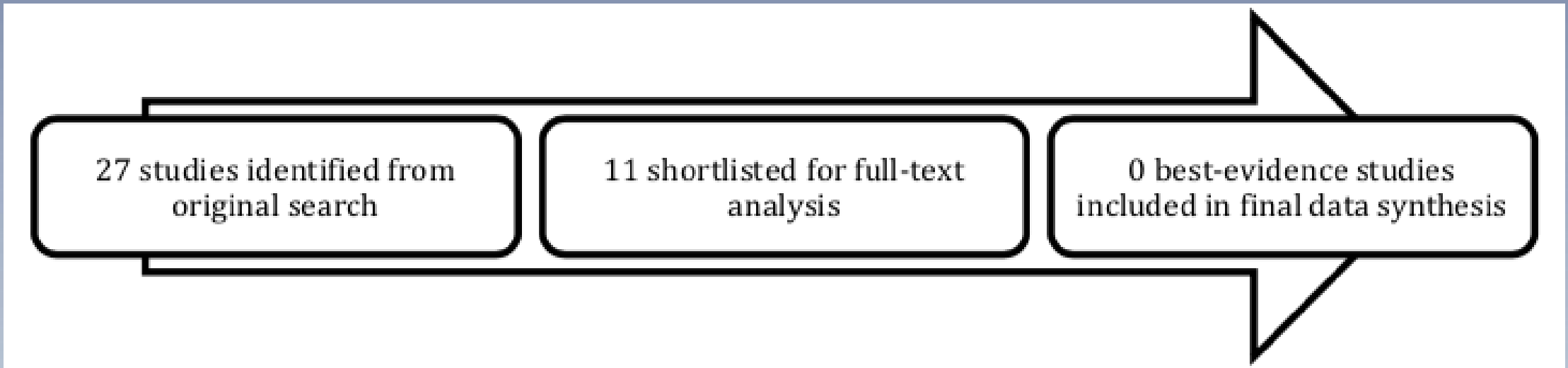
PICO #12


27 studies identified from original search
11 shortlisted for full-text analysis
0 best-evidence studies included in final data synthesis

PICO #12: Recommendation B1

- Current evidence is insufficient to make a recommendation in the difficult laparoscopic cholecystectomy regarding conversion vs no conversion to open cholecystectomy to limit/avoid bile duct injury.

- **Recommendations for future study/ type B Recommendation:**
- Recommendation B1: We suggest the conduct of prospective and retrospective comparisons of clinical outcomes of various ‘bail-out’ options for the difficult cholecystectomy that include conversion to open, subtotal cholecystectomy, and procedure abandonment.

Vote on PICO 12 B1 Recommendation

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PICO #12: Recommendation B2

- **Recommendations for future study/ type B Recommendation:**

- Recommendation B2: We suggest the development and establishment of valid evidence for a ‘procedure difficulty score’ for laparoscopic cholecystectomy.

Vote on PICO 12 B2 Recommendation

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PICO #13

- **PICO 13:** Should surgeons take a time out to verify the critical view of safety versus no time out be used for limiting the risk or severity of bile duct injury during laparoscopic cholecystectomy?
- No relevant data

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PICO #13


5 studies identified from original search
1 shortlisted for full-text analysis
0 best-evidence studies included in final data synthesis

PICO #13: Recommendation

- Recommendation A: Current evidence is insufficient to make a recommendation. However, as best practice, we suggest that during laparoscopic cholecystectomy, surgeons conduct a *momentary pause for the surgeon to confirm in his/her own mind that the criteria for the critical view of safety have been attained before clipping or transecting ductal or arterial structures*.
- **Recommendations for future study/ type B Recommendation:**
- Recommendation B: We suggest incorporation of a 'critical view time-out' in all prospective studies of laparoscopic cholecystectomy.

PICO #13: Recommendation

- Recommendation A: Current evidence is insufficient to make a recommendation. However, as best practice, we suggest that during laparoscopic cholecystectomy, surgeons conduct a *momentary pause for the surgeon to confirm in his/her own mind that the criteria for the critical view of safety have been attained* before clipping or transecting ductal or arterial structures.

Vote on PICO 13 A Recommendation

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PICO #13: Recommendation

- **Recommendations for future study/ type B Recommendation:**

- Recommendation B: We suggest incorporation of a ‘critical view time-out’ in all prospective studies of laparoscopic cholecystectomy.

Vote on PICO 13 B Recommendation

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PICO #14

- **PICO 14:** Should two surgeons versus one surgeon be used for limiting the risk of severity of bile duct injury during laparoscopic cholecystectomy?
- Primary Outcome – BDI

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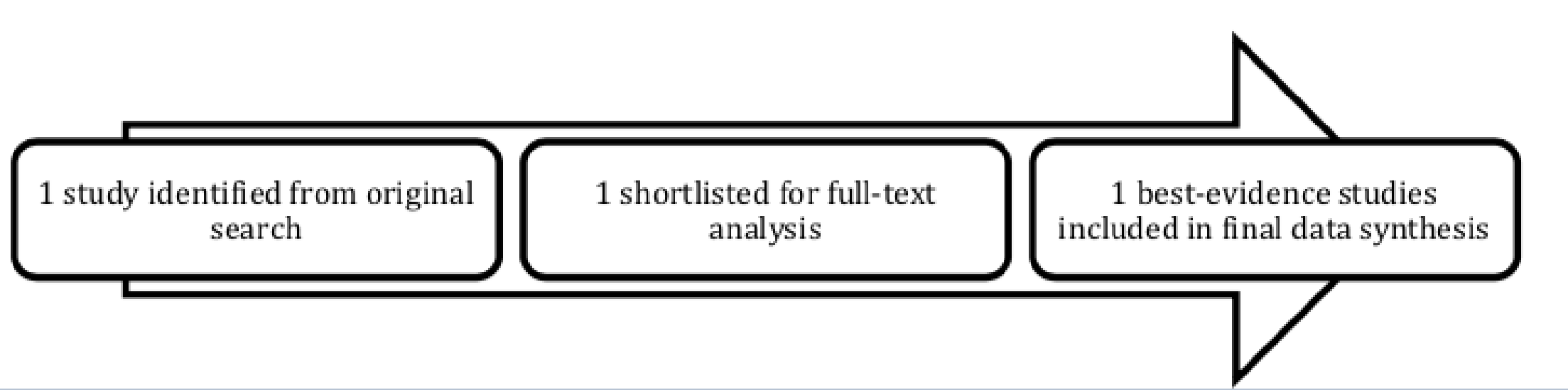
PICO #14


1 study identified from original search
1 shortlisted for full-text analysis
1 best-evidence studies included in final data synthesis

PICO #14

Summary
A single 2011 cohort study[1] of the Florida state database (1997-2006) assessed 231,502 cholecystectomies, comparing hospitals with residency programs (and therefore assuming resident involvement in the case) and those without residents. There was no difference in adjusted BDI rates, OR 1.021 (0.739 – 1.409). Hospitals with residency programs had higher unadjusted rates of conversion (9.1% vs. 7.5%, p<0.001), but no significant difference in mortality rates (0.4% vs. 0.6%, p=0.602)

PICO #14: Recommendation

- Current evidence is insufficient to make a recommendation regarding two vs one surgeons for limiting/avoiding bile duct injury in cholecystectomy.

References

[1] Harrison VL, Dolan JP, Pham TH, et al. Bile duct injury after laparoscopic cholecystectomy in hospitals with and without surgical residency programs: is there a difference? Surg Endosc. 2011 Jun;25(6):1969-74.

Work Group Six: PICO #18

Co-leads:

Horacio J Asbun, Jaap Bonjer, Rowan W Parks

Study Group

Lugi Boni

Ewan Harrison

Oscar Imventarza

Rohan Jeyarajah

Francisco Leon

Marc Mesleh

Levam Tsalamaidze

Eline Zwart D Asbun,

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PICO Question #18

Referral to a specialist with experience in biliary reconstruction

vs

Reconstruction by the operating surgeon for patients with bile duct injury during laparoscopic cholecystectomy

(in the OR or early postoperative period)

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PICO #18: Recommendations

When a bile duct injury (BDI) has occurred or is highly suspected at the time of cholecystectomy or in the post-operative period, we suggest:

The patient is promptly referred to a surgeon with experience in the management of BDI, in an institution with a hepato-biliary disease multispecialty team. When not feasible to do so in a timely manner, prompt consultation with a surgeon experienced in the management of BDI should be considered.

(strong recommendation, low certainty of evidence)

PICO #18: Summary of Literature Reviewed

- No RCTs
- No systematic reviews addressing the issue
- 3 retrospective comparative study
- 44 case series

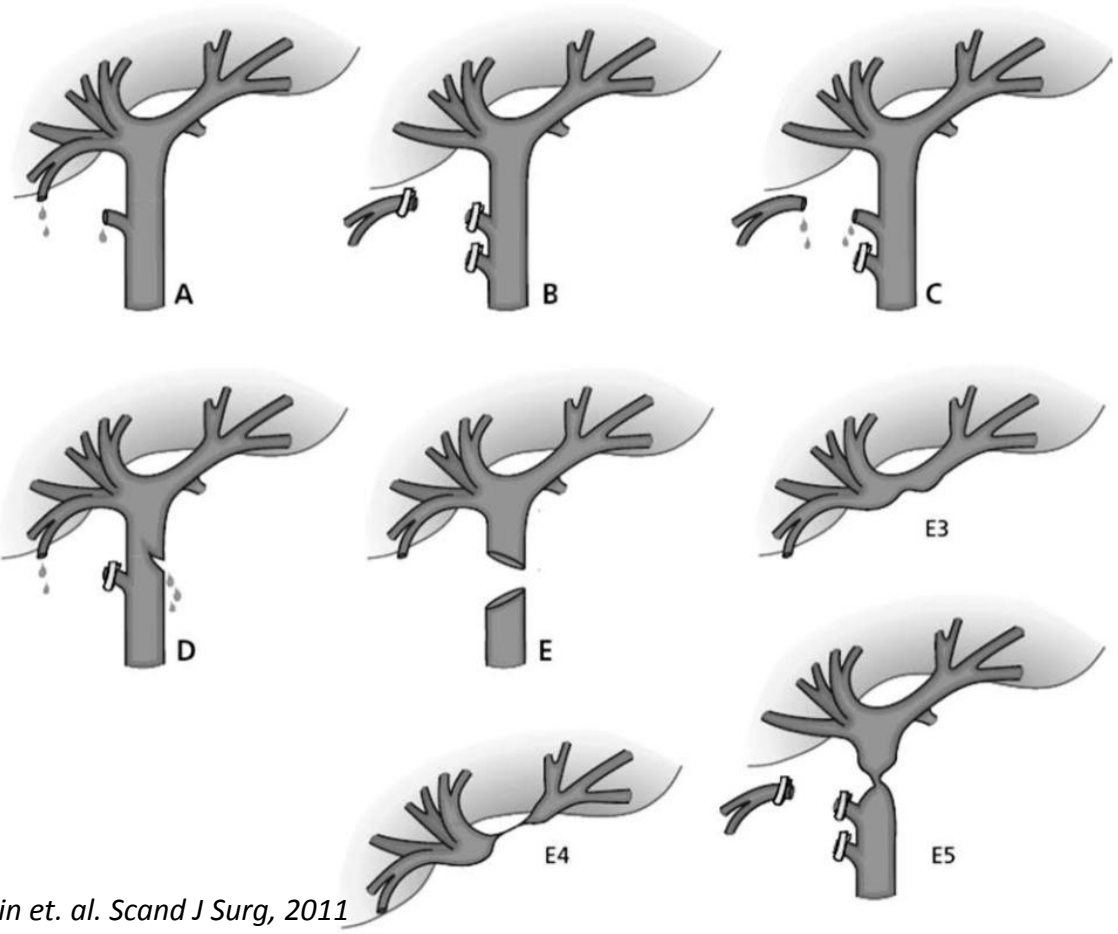
- Insufficient for meta analysis
- High variability of studies

PICO #18: Research Evidence

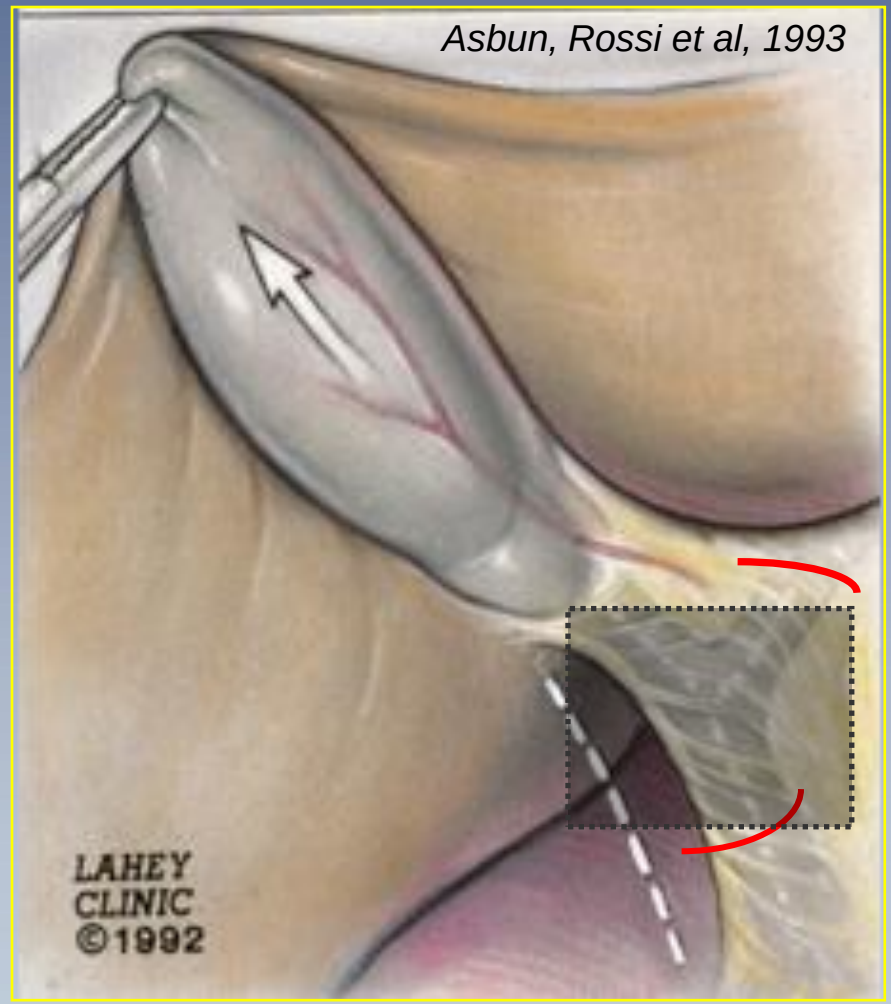
No Level I Evidence

- Majority of studies include only patients with BDI repaired at expert centers.
- Studies lack the denominator: How many patients were successfully repaired by the primary surgeon

BDI: Strasberg Classification



Nordin et. al. Scand J Surg, 2011



Asbun, Rossi et al, 1993

PICO #18: Research Evidence

- Perera MT et.al: Specialist early and immediate repair of post-laparoscopic cholecystectomy bile duct injuries is associated with improved long term outcome Ann of Surg 2011; 253: 553-560

Immediate and early repair by specialists after BDI

200 pts treated for major BDI w/ median f/u of 60 months

- During LC: 52% anatomy described as normal 30% difficult
- 72% major type E injury, 13% type D
- 25% on-table repairs done by “outreach” team

PICO #18: Research Evidence

- Perera MT et.al: Specialist early and immediate repair of post-laparoscopic cholecystectomy bile duct injuries is associated with improved long term outcome Ann of Surg 2011; 253: 553-560

Immediate and early repair by specialists after BDI

TABLE 5. Summary of Outcomes After Surgical Intervention to BDI; Results by Surgeon Group

	Non-HBS (n = 45)	HBS (n = 112)	Significance (Fisher Exact Test)
Stricture (%)	31 (69%)	19 (17%)	< 0.001
Recurrent cholangitis (%)	15 (33%)	12 (11%)	< 0.001
Intervention/dilatation (%)	23 (51%)	16 (14%)	< 0.001
Redo reconstruction (%)	24 (53%)	4 (3%)	< 0.001
Overall morbidity (%)	37 (82%)	28 (25%)	< 0.001

PICO #18: Research Evidence

- Sicklick J et.al: **Surgical management of Bile Duct Injuries Sustained during laparoscopic cholecystectomy** Ann of Surg 2005; 241: 786-795

Early referral to experienced multispecialty team appears to obtain optimal results

200 pts treated for major BDI (mainly a descriptive series)

- 44% (81/188) outside referrals underwent sx prior to referral
- 58% referred within 1 month. (> incidence of bile leak, cholangitis) Median time to referral 3wks
- 175 pts had surgical repair: 98% R-Y hep-jej

PICO #18: Research Evidence

- Thomson BNJ et al: **Early specialist repair of biliary injury** Br J Surg 2006; 93: 216-20

Immediate repair by experienced team offers the best chance

123 BDI: 87 during LC

- 55 pts attempted repair prior to referral
  - 78% required revision
- 89% success rate (42/47) in experienced unit
- In selected patients, early repair = delayed repair

PICO #18: Research Evidence
Minor Injuries

J Rystedt et al: **Bile duct injuries associated with 55,134 cholecystectomies: Treatment & Outcome from a National perspective** World J Surg 2016; 40: 73-80

Repaired by operating surgeon: Short term outcomes "surprisingly good"

174 BDI in 55,134 LC (0.3%)

- 140/155 repaired immediately
- 59%Hannover Grade C 1 < 5mm lesion
- 17% pts had a R-Y Hep-jej

PICO #18: Recommendations
How to implement? All involved parties

-Establishing fast tract BDI referral pathways to offer advice and contribute to immediate treatment strategies.

-Share recommendation through residency training, society guidelines, oral presentations at meetings, scientific manuscripts and <u>incorporation of the concept:</u>

- ***Referring patient implies good judgment, not a failure***

PICO #18: Research Evidence

- Silva MA et al: **Specialist outreach service for on-table repair of iatrogenic bile duct injuries - a new kind of "travelling surgeon"** Ann R Coll Engl 2008; 90: 243-6

Repair of BDI as an outreach is feasible and safe

22 BDI: <u>20 with classical excision injury</u>

- 95% had R-Y repair
- 2 Bile leaks, 1 transient jaundice
- 1 pt required transfer (associated hepatic artery injury)
- 14% required PTCH + dilatation 6-28m post op

PICO #18: Recommendations
Justification Summary

- **Strong clinical rationale and indirect evidence favoring specialty repair despite of very low certainty direct evidence exists addressing this question.**
- **Complexity in assessing extent of BDI/VI and the type of surgery entailed in the repair is significantly different than LC**
- **Experience for LC cannot be generalized to repairs of BDI.**

PICO #18: Recommendations
Justification Summary

- **No concerns were noted by the panel regarding the generalizability of the systematic review evidence.**
- **Undesirable effects secondary to a potential delay related to a specialist referral were considered small or trivial, contingent to preparing the patient well for such a referral/transfer** i.e. placement of drains
- **Balance of benefit and harms were judged to strongly favor the intervention.**

PICO #18: Recommendations:

When a bile duct injury (BDI) has occurred or is highly suspected at the time of cholecystectomy or in the post-operative period, we suggest:

The patient is promptly referred to a surgeon with experience in the management of BDI, in an institution with a hepato-biliary disease multispecialty team. When not feasible to do so in a timely manner, prompt consultation with a surgeon experienced in the management of BDI should be considered.

(strong recommendation, low certainty of evidence)

Vote on PICO 18 Recommendation

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