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Original Article

Role of prophylactic antibiotics in elective laparoscopic cholecystectomy: A systematic review and meta-analysis

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Backgrounds/Aims: The role of prophylactic antibiotics for laparoscopic cholecystectomy in low-risk patients is still unclear. This study aimed to verify the conclusion of previous meta-analyses concerning the effectiveness of antibiotic prophylaxis for elective laparoscopic cholecystectomy in low-risk patients. **Methods:** Comprehensive literature searches were performed on electric databases and manual searches. Randomized controlled trials (RCTs), prospective studies, and retrospective studies comparing antibiotic prophylaxis to placebo or no antibiotics in low-risk elective laparoscopic cholecystectomy were included. **Results:** This study included 28 RCTs, three prospective studies, and three retrospective studies. In RCTs, prophylactic antibiotics did not prevent deep surgical site infections (SSI) (RR 1.10, 95% confidence interval [CI] [0.45-2.69], p=0.84) but reduced SSI (RR 0.70, 95% CI [0.53-0.94], p=0.02), and superficial SSI (RR 0.58, 95% CI [0.42-0.82], p=0.01). Prospective studies showed prophylactic antibiotics did not reduce superficial SSI (RR 0.35, 95% CI [0.01-8.40], p=0.52) but reduced SSI (RR 0.12, 95% CI [0.04-0.35], p=0.0001). In retrospective studies, antibiotic prophylaxis did not reduce SSI (RR 1.59, 95% CI [0.30-8.32], p=0.58). The pooled data (12121 patients) including RCTs and prospective and retrospective studies showed that prophylactic antibiotics were not effective in preventing deep SSI (RR 1.01 95% CI [0.46-2.21], p=0.98) but effective in reducing SSI (RR 0.67, 95% CI [0.51-0.88], p=0.003) and superficial SSI (RR 0.61, 95% CI [0.45-0.83], p=0.002). **Conclusions:** The use of prophylactic antibiotics is effective for reducing the incidence of SSI and superficial SSI but is not effective for preventing deep SSI in low-risk patients who underwent elective laparoscopic cholecystectomy. **(Ann Hepatobiliary Pancreat Surg 2018;22:231-247)**

Key Words: Laparoscopic cholecystectomy; Antibiotic prophylaxis; Meta-analysis

INTRODUCTION

Laparoscopic cholecystectomy is the gold standard method in managing uncomplicated gallbladder stones and other benign gallbladder diseases over open cholecystectomy. Development of minimally invasive laparoscopic cholecystectomy reduced surgical site infection (SSI), length of hospital stay, healthcare costs, and postoperative pain.

Although the use of prophylactic antibiotics before elective surgery has been considered as the best way to prevent postoperative infectious complications, antibiotic prophylaxis for elective laparoscopic cholecystectomy in low-risk group is not recommended in recent guidelines on SSI from the Scottish Intercollegiate Guidelines Network and the American Society of Health-System Pharmacists.[1,2] Nevertheless, low-risk patients who underwent laparoscopic cholecystectomy are still given prophylactic antibiotics in several clinical centers.

Recent meta-analyses[3-13] investigating the effects of prophylactic antibiotics before elective laparoscopic cholecystectomy for the prevention of SSI have relatively small sample size and low statistical power. Moreover, controversy still exists regarding the effectiveness of anti-

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biotic prophylaxis for elective laparoscopic cholecystectomy. Therefore, we performed an up-to-date meta-analysis to assess the value of prophylactic antibiotics for low-risk elective laparoscopic cholecystectomy in terms of reducing the incidence of SSI, superficial SSI, and deep SSI with randomized controlled trials (RCTs) and prospective and retrospective studies on this topic. This study aimed to verify the conclusion of previous meta-analyses.[3-13]

MATERIALS AND METHODS

The study protocol for this systemic review and meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines.[14]

Searching and other resources

MEDLINE, Embase, the Cochrane Central Register of Controlled Trials, PubMed, and KMbase were searched using medical subject heading terms and following keyword combinations: "laparoscopic," "cholecystectomy," "antibiotic," "prophylac," and "meta-analysis." Table 1 shows the search strategies on electric databases in this review. Additionally, manual searches were performed with reference lists of original articles and systemic review and meta-analyses. The literature search was limited to articles published between 1995 and 2018 without restriction of languages.

Inclusion and exclusion criteria

Inclusion criteria were (i) study design: RCTs and prospective and retrospective studies evaluating the effective-

Table 1. Search strategies

Database	Search strategies
MEDLINE 1995 to July 2018 (N=441)	1. cholecystectom*.mp or exp cholecystectomy 2. laparoscop*.mp or exp cholecystectomy, laparoscopic 3. 1 OR 2 4. prophyla*.mp or exp Antibiotic Prophylaxis 5. antibiotic*.mp or exp Anti-Bacterial Agents 6. 4 OR 5 7. 3 AND 6 8. limit: Publication Year 1995−Current mp=title, original title, abstract, name of substance word, subject heading word, unique identifier
EMBASE 1995 to July 2018 (N=417)	1. cholecystectom*.mp or exp cholecystectomy 2. laparoscop*.mp or exp cholecystectomy, laparoscopic 3. 1 OR 2 4. prophyla*.mp or exp Antibiotic Prophylaxis 5. antibiotic*.mp or exp Anti-Bacterial Agents 6. 4 OR 5 7. 3 AND 6 8. limit: Publication Year 1995−Current mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer
Cochrane Library 1995 to July 2018 (N=249)	#1 Mesh descriptor: [Cholecystectomy, Laparoscopic] explode all trees #2 Mesh descriptor: [Anti-Bacterial Agents] explode all trees #3 prophyla* or perioperative or peri-operative #4 (#2 or #3) #5 (#1 and #3)
PubMed 1995 to July 2018 (N=363)	#1 laparoscopic cholecystectom*[Title/Abstract] #2 antibiotic[Title/Abstract] #3 Prophylac*[Title/Abstract] OR Prophylaxis[Title/Abstract] #4 (#2 OR #3) #5 (#1 AND #4) Filters: Publication date from 1995/01/01 to 2018/07/15
KMbase 1995 to 2018 (N=2)	1. laparoscopic cholecystectomy antibiotic 2. cholecystectomy antibiotic

ness of antibiotic prophylaxis for elective laparoscopic cholecystectomy with placebo or untreated controlled group; (ii) population: low-risk patients undergoing elective laparoscopic surgery; (iii) all patients that were given antibiotics before operation and/or postoperative days; (iv) all studies having at least one of the following outcome parameters: SSI, superficial SSI and deep SSI.

Exclusion criteria were (i) studies that are not full-text original articles and (ii) interventions comparing different antibiotic prophylaxis groups without placebo or untreated groups.

SSIs include superficial and deep, and data were collected based on the definition of guideline.[15,16] High-risk factors for SSI are defined according to the diabetes, obesity, open conversion, emergency operation, preoperative endoscopic or percutaneous biliary intervention, acute cholecystitis, intraoperative gallbladder rupture, obstructive jaundice, immunosuppression, insertion of prosthetic device, and episode of colic within 30 days in guideline.[1,2]

Data collection and analysis

This systemic review and meta-analysis was performed following the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions.[17]

Study selection

Two reviewers (Kim and Yu) independently searched available articles to include eligible RCTs and prospective and retrospective studies. Duplicate articles were removed. The full-text articles of possibly related studies were selected to make a list of trials that fulfilled the inclusion criteria. Disagreements about study selection were resolved through discussion and consensus.

Data extraction

The following data were extracted independently by two reviewers (Kim and Yu) from each study when present: inclusion and exclusion criteria, characteristic of population, study design, type of prophylactic antibiotics and dosage, schedule of administration of antibiotics, randomization method, allocation concealment, number of randomized patients in RCTs and enrolled patients in prospective and retrospective studies, drop-outs, intention-to-treat analysis or per-protocol analysis, SSIs, and superficial and deep infections.

Quality assessment of the studies

Two investigators (Kim and Yu) independently assessed the quality of RCTs included through assessing the following risks of bias check lists provided by The Cochrane Collaboration[18]: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases. Risk of bias was assessed as high, low, and unclear. Jadad et al.[19] score was also applied to assess the quality of included randomized studies in the meta-analysis. Of the 28 RCTs,[20-47] 25 studies[22-37,39-47] were eligible to be included in the meta- analysis with high-quality Jadad score ≥ 3, and the other 3 studies[20,21,38] were low-quality studies with Jadad score 2. Sensitivity tests were performed to assess whether including three RCTs classified as low-quality is appropriate in this meta-analysis.

Non-RCTs including 3 prospective[48-50] and 3 retrospective[22,51,52] studies were assessed based on the Newcastle-Ottawa Scale,[53] which ranges from 0 to 9, with "high quality" defined as a Newcastle-Ottawa Scale total score ≥ 7. Of the 6 non-RCTs included in this meta-analysis, 2 prospective studies were classified as "high quality." Sensitivity tests were performed to obtain pooled data rate. Disagreements about assessment were resolved through discussion and consensus.

Statistical analysis

Statistical analyses were conducted using Review Manager version 5.3 (The Cochrane Collaboration). In dichotomous variable analysis, the effect size of the intervention was represented by risk ratio (RR) with 95% confidence interval (CI) and was calculated for continuous variables. A random effect model was applied to calculate the estimated pooled event rate in the presence of significant heterogeneity, determined either when the I^2 value was $>50\%$ or p-value of Cochrane Q test was <0.1. The publication bias was evaluated to detect "small-study effects" by funnel plot.[54] RCTs and prospective and retrospective studies were pooled separately to minimize the bias. Sensitivity analysis was performed to assess whether including non-randomized studies or low-quality studies is appropriate in this meta-analysis.[17]

RESULTS

Study selection

A total of 1472 studies were screened through electronic database using our search strategies in July 2018. And 1096 articles were found by hand search. After investigation of title and abstract, 239 articles were screened. Full texts of 63 articles were reviewed and assessed for eligibility, and 34 studies including 28 RCTs and 3 prospective and 3 retrospective trials were included in this meta-analysis. Twenty-nine full-text articles[55-84] were excluded because of the following reasons: inclusion criteria not met,[83] inappropriate intervention,[55,57,70,77,84] inappropriate comparator,[56,58,59] insufficient data reported,[60,61,63,65-69,71-76,78,80-82] and data duplication.[62,64] The procedure for the study selection is summarized in the PRISMA flow diagram (Fig. 1).

Study characteristics

The 12121 patients who underwent laparoscopic cholecystectomy from eligible 28 RCTs with 7770 patients, 3 prospective studies with 3123 patients, and 3 retrospective studies with 1228 patients were included in this meta-analysis. Table 2 shows a summary of the characteristics of the included studies published between 1995 and 2018, including years of publication, country, language, study design, intervention, sample size, type of data collection analysis, follow-up days, and outcomes. Most of the patients included in RCTs were classified as low risk for postoperative infection. Exclusion criteria in the majority of RCTs were ASA physical status classification III or higher, antibiotics use within 7 days of the surgery, allergy, complicated gallstone with acute cholecystitis, choledocholithiasis or pancreatitis, previous biliary tract surgery, conversion to open cholecystectomy, diabetes mellitus, immunosuppression, pregnancy, prosthetic heart valve, severe comorbidities such as Child C liver cirrhosis

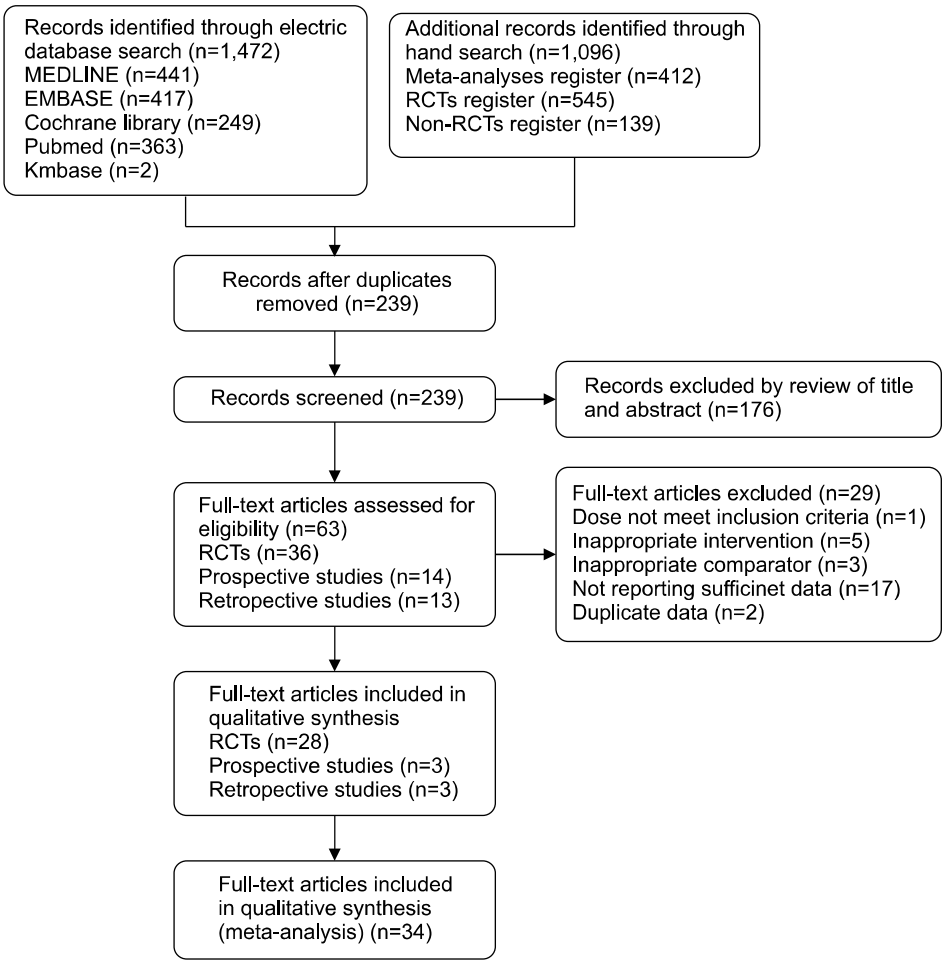

Fig. 1. PRISMA flow diagram for study search.

Table 2. Characteristics of included studies

Study	Year	Country	Language	Center	No. of patients	Antibiotic	Injection	Dose	Control	Follow-up (days)	Data collection	SSI	Superficial SSI	Deep SSI
RCTs														
Csendes et al.[20]	1995	Chile	Portuguese	Single	50	Cefazolin 1 g	Pre	1	Untreated	14	PP	2	-	-
					55	No prophylaxis						2	-	-
Illig et al.[21]	1997	US	English	Single	128	Cefazolin 1 g OR vancomycin	Pre & post	3	Untreated	30	ITT	0	0	0
					122	No prophylaxis						1	1	0
Higgins et al.[23]	1999	US	English	Single	137	Cefotetan 1 g	Pre	1	Placebo	30	PP	3	3	0
					140	Cefazolin 1 g	Pre	1	Placebo	30		2	2	0
					135	No prophylaxis						2	2	-
Dobay et al.[22]	1999	US	English	Single	29	Cefotetan 1 g	Pre	1	Placebo	30	ITT	0	0	-
					24	No prophylaxis						0	0	-
Harling et al.[24]	2000	UK	English	Single	39	Cefuroxime 750 mg	Pre	1	Untreated	NA	PP	3	-	-
					37	No prophylaxis						3	-	-
Tocchi et al.[25]	2000	Italy	English	Single	44	Cefotaxime 2 g	Pre & post	2	Placebo	42	PP	4	-	1
					40	No prophylaxis						4	-	0
Mahatharadol[26]	2001	Thailand	English	Single	50	Cefazolin 1 g	Pre	1	Untreated	30	PP	0	0	0
					50	No prophylaxis						1	1	0
Koc et al.[27]	2003	Turkey	English	Single	49	Cefotaxime 2 g	Pre & post	2	Placebo	30	PP	1	-	-
					43	No prophylaxis						1	-	-
Chang et al.[28]	2006	Taiwan	English	Single	141	Cefazolin 1 g	Pre	1	Placebo	28	ITT	2	1	1
					136	No prophylaxis						2	2	0
Kuthe et al.[29]	2006	India	English	Single	40	Cefuroxime 1.5 g	Pre	1	Placebo	28	PP	1	1	0
					53	No prophylaxis						2	1	1
Souza et al.[30]	2008	Brazil	Portuguese	Single	82	Cefoxitin 2 g	Pre	1	Placebo	28	ITT	4	2	2
					81	No prophylaxis						5	3	2
Uludag et al.[31]	2009	Turkey	English	Single	68	Cefazolin 1 g	Pre	1	Placebo	30	PP	3	3	0
					76	No prophylaxis						2	2	0
Yildiz et al.[32]	2009	Turkey	English	Single	105	Cefazolin 1 g	Pre	1	Placebo	30	ITT	4	3	1
					103	No prophylaxis						3	3	0
Gaur and Pujahari[33]	2010	India	English	Multi	208	Ciprofloxacin 200 mg + Metronidazole 500 mg	Pre	1	Placebo	30	PP	5	0	5
					209	No prophylaxis						8	4	4
Sharma et al.[34]	2010	India	English	NA	50	Ceftriaxone 1 g	Pre	1	Placebo	50	PP	2	2	0
					50	No prophylaxis						4	4	0

Table 2. Continued

Study	Year	Country	Language	Center	No. of patients	Antibiotic	Injection	Dose	Control	Follow-up (days)	Data collection	SSI	Superficial SSI	Deep SSI
Al-Qahtani[35]	2011	Saudi Arabia	English	Single	112	Cefuroxime 1.5 g	Pre	1	Untreated	30	PP	3	3	0
					119	No prophylaxis						5	5	0
Shah et al.[37]	2012	Nepal	English	Single	154	Cefazolin 1 g	Pre	1	Untreated	7	PP	6	6	-
					156	No prophylaxis						9	9	-
Hassan et al.[36]	2012	Egypt	English	Single	100	Ceftazidime	Pre	1	Placebo	30	ITT	2	2	0
					100	No prophylaxis						1	1	0
Naqvi et al.[38]	2013	Pakistan	English	Single	177	Cefuroxime 1.5 g	Pre	1	Untreated	28	ITT	8	8	0
					173	No prophylaxis						7	7	0
Turk et al.[39]	2013	Turkey	English	Single	278	Cefazolin 1 g	Pre	1	Placebo	30	PP	4	-	-
					269	No prophylaxis						2	-	-
Matsui et al.[40]	2014	Japan	English	Single	518	Cefazolin 1 g	Pre & post	3	Untreated	>8	ITT	4	4	0
					519	No prophylaxis						19	16	3
Mirani et al.[41]	2014	Pakistan	English	Single	154	Cefazolin 1 g	Pre	1	Untreated	7	PP	6	6	-
					156	No prophylaxis						9	9	-
Ruangsin et al.[42]	2014	Thailand	English	Single	150	Cefazolin 1 g	Pre	1	Placebo	30	ITT	2	2	0
					149	No prophylaxis						5	5	0
Darizi et al.[43]	2016	Iran	English	Single	182	Cefazolin 1 g	Pre & post	3	Placebo	30	ITT	3	3	0
					247	No prophylaxis						5	5	0
Passos and Portari-Filho[44]	2016	Brazil	English	Single	50	Cefazolin 2 g	Pre	1	Untreated	30	ITT	1	-	-
					50	No prophylaxis						1	-	-
Sarkut et al.[46]	2017	Turkey	English	Single	191	Cefazolin 1 g	Pre	1	Placebo	28	PP	2	2	0
					186	Cefuroxime 750 mg	Pre	1	Placebo	28		2	2	0
					193	No prophylaxis						3	3	0
Kim et al.[45]	2017	Korea	English	Single	81	Cefazolin 1 g	Pre	1	Placebo	Once	ITT	0	0	0
					82	No prophylaxis						0	0	0
Nauman et al.[47]	2018	Pakistan	English	Single	325	Cefuroxime 1.5 g	Pre	1	NA	21	ITT	4	4	-
					325	No prophylaxis				21		13	13	-
Prospective studies														
Lippert and Gastinger[48]	1998	Germany	English	Multi	739	Ceftriaxone	Pre	1	NA		-	1	-	-
					949	Other antibiotics	Pre	1	NA			2	-	-
					1195	No prophylaxis						21	-	-

Table 2. Continued

Study	Year	Country	Language	Center	No. of patients	Antibiotic	Injection	Dose	Control	Follow-up (days)	Data collection	SSI	Superficial SSI	Deep SSI
Han et al.[50]	2008	Korea	Korean	Single	77	2nd cefalosporin	NA	NA	Untreated	NA	-	0	0	0
					28	No prophylaxis						0	0	0
Guzman-Valdivia[49]	2008	Mexico	English		80	Cefotaxime 1 g	pre/post 8 hr, 16 hr	3		30	-	0	0	0
					86	No prophylaxis						1	1	0
Retrospective studies														
Garcia et al.[51]	1997	US	English	Single	110	Several antibiotics	Pre	1	NA	NA	-	0	-	-
					81	No prophylaxis						1	-	-
Dobay et al.[22]	1999	US	English		328	NA			NA	NA	-	10	-	-
					238	No prophylaxis						1	-	-
Chong et al.[52]	2015	Korea	English		273	2nd Cefalosporin 1 g	Pre	1	Untreated	48	-	5	5	0
					185	No prophylaxis				48		3	3	0

RCTs, randomized controlled trials; SSI, surgical site infections; NA, not available; PP, Per-protocol analysis; ITT, Intention-to-treat analysis

or end-stage renal disease, body mass index >30, and age >70 years or <14 years. However, in the definition of high-risk patients, the criteria of ASA score, BMI, and old age are not exactly the same in included studies.

Risk of bias and Jadad score for RCTs included in this meta-analysis are summarized in Tables 3 and 4 shows the Newcastle-Ottawa Scale for non-RCTs included in this review. In RCTs, only 12 studies[21,22,28,32,36,38,40,42-45,47] showed the data from intention-to-treat analysis, and the other 16 studies[20,23-27,29-31,33-35,37,39,41,46] showed data from per-protocol analysis.

Surgical site infections

Subgroup analysis for SSI including both superficial and deep SSI was performed using 28 RCTs,[20-47] 3 prospective studies,[48-50] and 3 retrospective studies.[22,51,52] In the 28 RCTs, 83 (2.07%) of the 4018 patients in the prophylactic antibiotic group developed SSI compared with 119 (3.17%) of the 3752 patients in the no prophylaxis group. The prophylactic antibiotic group had less incidence of SSI than the control group (RR 0.70, 95% CI [0.53-0.94], p=0.02) without significant heterogeneity (p=0.96, I^2=0%). In 3 prospective studies, 3 (0.16%) of the 1831 patients in the prophylactic antibiotic group developed SSI compared with 22 (1.70%) of the 1292 patients in the no prophylaxis group. The patients in the prophylactic antibiotic group had less incidence of SSI than the control group (RR 0.12 [0.04-0.37], p=0.0002). No significant heterogeneity was found among included prospective studies (p=0.48, I^2=0%). In 3 retrospective studies, 15 (2.09%) of the 717 patients in the prophylactic antibiotic group developed SSI compared with 5 (0.98%) of the 511 patients in the no prophylaxis group. No significant difference was observed in the incidence of SSI between the prophylactic antibiotic group and the control group (RR 1.59, 95% CI [0.30-8.32], p=0.58) without significant heterogeneity among included prospective studies (p=0.58, I^2=47%). In the overall pooled event rate including 28 RCTs and 3 prospective studies and 3 retrospective studies, 101 (1.54%) of the 6566 patients in the prophylactic antibiotic group developed SSI compared with 146 (2.63%) of the 5555 patients in the no prophylaxis group. The patients in the prophylactic antibiotic group had less incidence of SSI than the control group (RR 0.67, 95% CI [0.51-0.88], p=0.003). No significant heterogeneity

Table 3. Risk of bias and Jadad score of included randomized controlled trials

Study	Random sequence generation	Allocation concealment	Blinding of participants & personnel	Blinding of outcome assessment	Incomplete outcome data	Selection reporting	Other bias	Jadad socre
Csendes et al.[20]	?	-	?	?	-	?	+	2
Illig et al.[21]	?	?	?	?	+	?	+	2
Higgins et al.[23]	?	+	-	-	-	?	+	3
Dobay et al.[22]	+	?	+	+	+	?	+	4
Harling et al.[24]	?	-	-	?	-	?	+	4
Tocchi et al.[25]	+	?	+	+	-	?	+	5
Mahatharadol[26]	+	?	-	-	-	?	+	3
Koc et al.[27]	?	?	+	+	-	?	+	4
Chang et al.[28]	+	?	+	+	+	?	-	5
Kuthe et al.[29]	+	?	+	+	-	?	+	5
Souza et al.[30]	?	?	+	+	+	?	+	4
Uludag et al.[31]	?	+	+	+	-	?	+	4
Yildiz et al.[32]	?	?	+	+	+	?	+	4
Gaur and Pugahari[33]	?	-	?	?	-	?	+	4
Sharma et al.[34]	?	-	-	-	-	?	+	3
Al-Qahtani[35]	+	+	?	?	-	?	+	3
Shah et al.[37]	+	-	?	?	-	?	+	3
Hassan et al.[36]	?	+	+	+	+	?	+	4
Naqvi et al.[38]	?	?	?	?	+	?	+	2
Turk et al.[39]	?	?	+	+	-	?	+	4
Matsui et al.[40]	+	+	+	+	+	?	+	5
Mirani et al.[41]	+	-	?	?	-	?	+	3
Ruangsin et al.[42]	+	+	+	+	+	?	+	5
Darizi et al.[43]	?	+	+	+	+	?	+	5
Passos and Portari-Filho[44]	+	+	+	+	+	?	+	5
Sarkut et al.[46]	+	+	+	+	-	?	+	5
Kim et al.[45]	+	?	?	+	+	?	+	3
Nauman et al.[47]	+	?	?	?	+	?	+	3

+, Low risk of bias; -, High risk of bias; ?, unclear risk of bias

Table 4. Newcastle-Ottawa Scale of included non-randomized studies

Prospective	Selection				Comparability	Outcome			Total score (0-9)
	Representativeness of case	Selection of nonexposed cohort	Ascertainment of exposure	Outcome of internest not present at start of study	Comparabiliry of cases and controls on the basis of the design or analysis	Assessment of outcome	Follow-up long enough for outcomes to occur	Adequacy of follow up of cohort	
Lippert and Gastinger[48]	★	★	-	★	★★	-	★	★	7
Han et al[50]	★	★	-	★	★★	-	-	-	5
Guzman-Valdivia[49]	★	★	-	★	★★	-	★	★	7
Retrospective	Selection				Comparability	Exposure			Total score (0-9)
	Adequate definition of case	Representativeness of cases	Selection of controls	Definition of controls	Study controls for important factor or additional factor	Ascertainment of exposure	Same method of ascertainment for cases and controls	Non-Response rate	
Garcia et al.[51]	★	-	-	★	★	-	★	-	4
Dobay et al.[22]	-	★	★	★	★	★	★	-	6
Chong et al.[52]	-	★	-	★	★★	★	★	-	6

among included studies was presented (p=0.47, I^2=0%) (Fig. 2).

Superficial surgical site infections

The incidence of superficial SSI was described in 22 RCTs,[21-23,26,28-38,40-43,45-47] 2 prospective studies,[49,50] and 1 retrospective study.[52] In 22 RCTs, 59 (1.68%) of the 3508 patients of the prophylactic antibiotic group developed superficial SSI compared with 96 (2.95%) of the 3258 patients in the no prophylaxis group. The patients in the prophylactic antibiotic group had less incidence of superficial SSI than the patients in the control group (RR 0.59, 95%

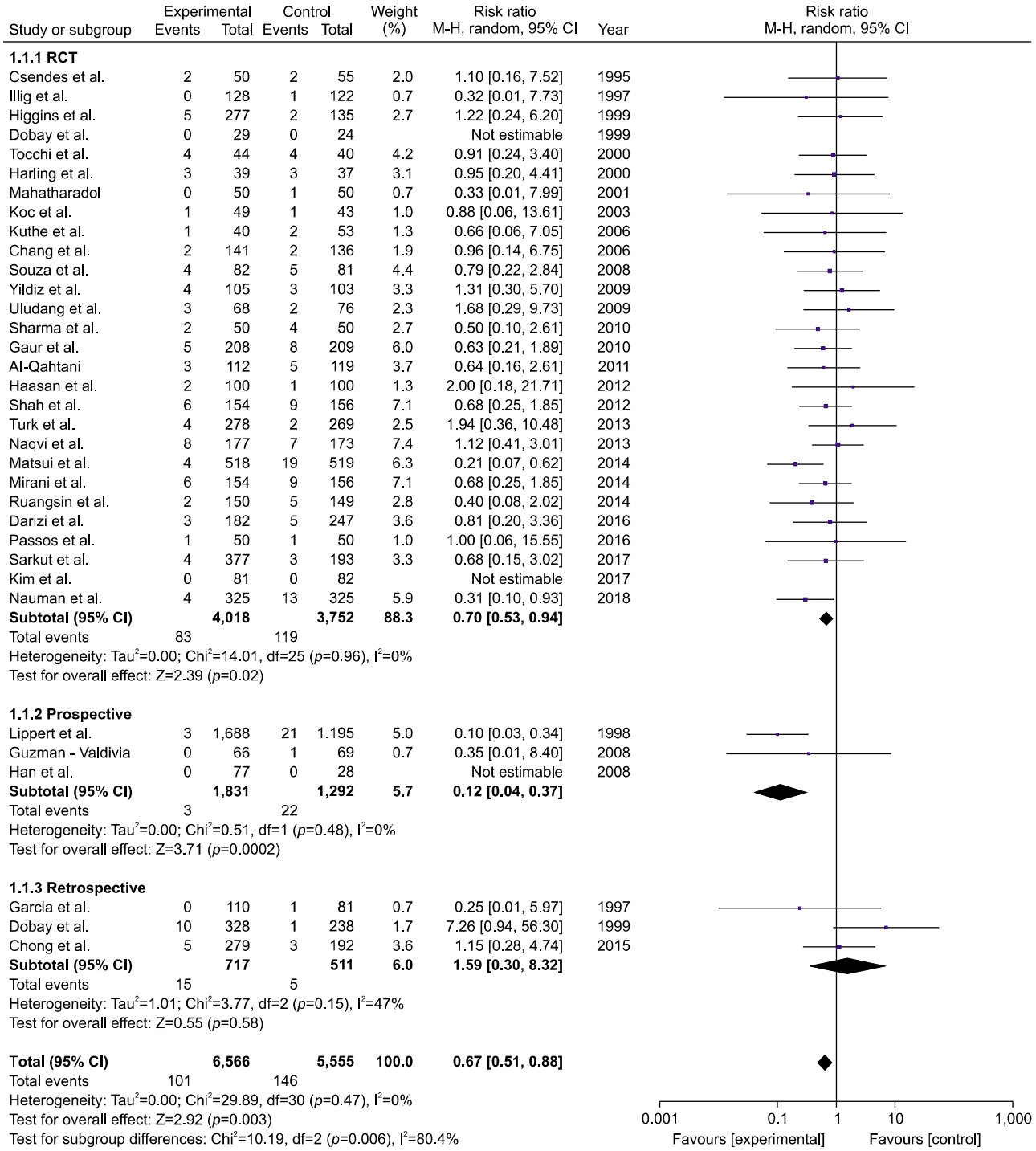

Fig. 2. Forest plot for surgical site infections in low-risk patients undergoing elective laparoscopic cholecystectomy. A Mantel-Haenszel fixed-effect model was for used for meta-analysis. Risk ratios are shown 95% confidence intervals.

CI [0.43-0.82], p=0.001) without significant heterogeneity among included studies (p=0.91, I^2=0%). In 2 prospective studies, 0 (0%) of the 143 patients in the prophylactic antibiotic group developed superficial SSI compared with 1 (1.03%) of the 97 patients in the no prophylaxis group. No difference was observed in outcomes between the two groups (RR 0.35 95% CI [0.01-8.40], p=0.52). In a retrospective study, 5 (1.79%) of the 279 patients in the prophylactic antibiotic group developed SSI compared with 3 (1.56%) of the 192 patients in the no prophylaxis group. In the overall pooled event rate including 22 RCTs, 2 prospective studies, and one retrospective study, 64 (1.63%) of the 3930 patients in the prophylactic antibiotic group developed superficial SSI compared with 100 (2.81%) of the 3547 patients in the no prophylaxis group. The prophylactic antibiotic group had less incidence of superficial SSI than the control group (RR 0.61, 95% CI [0.45-0.83], p=0.002). No significant heterogeneity was found among included studies (p=0.94, I^2=0%) (Fig. 3).

Deep surgical site infections

The incidence of deep SSI was described in 19

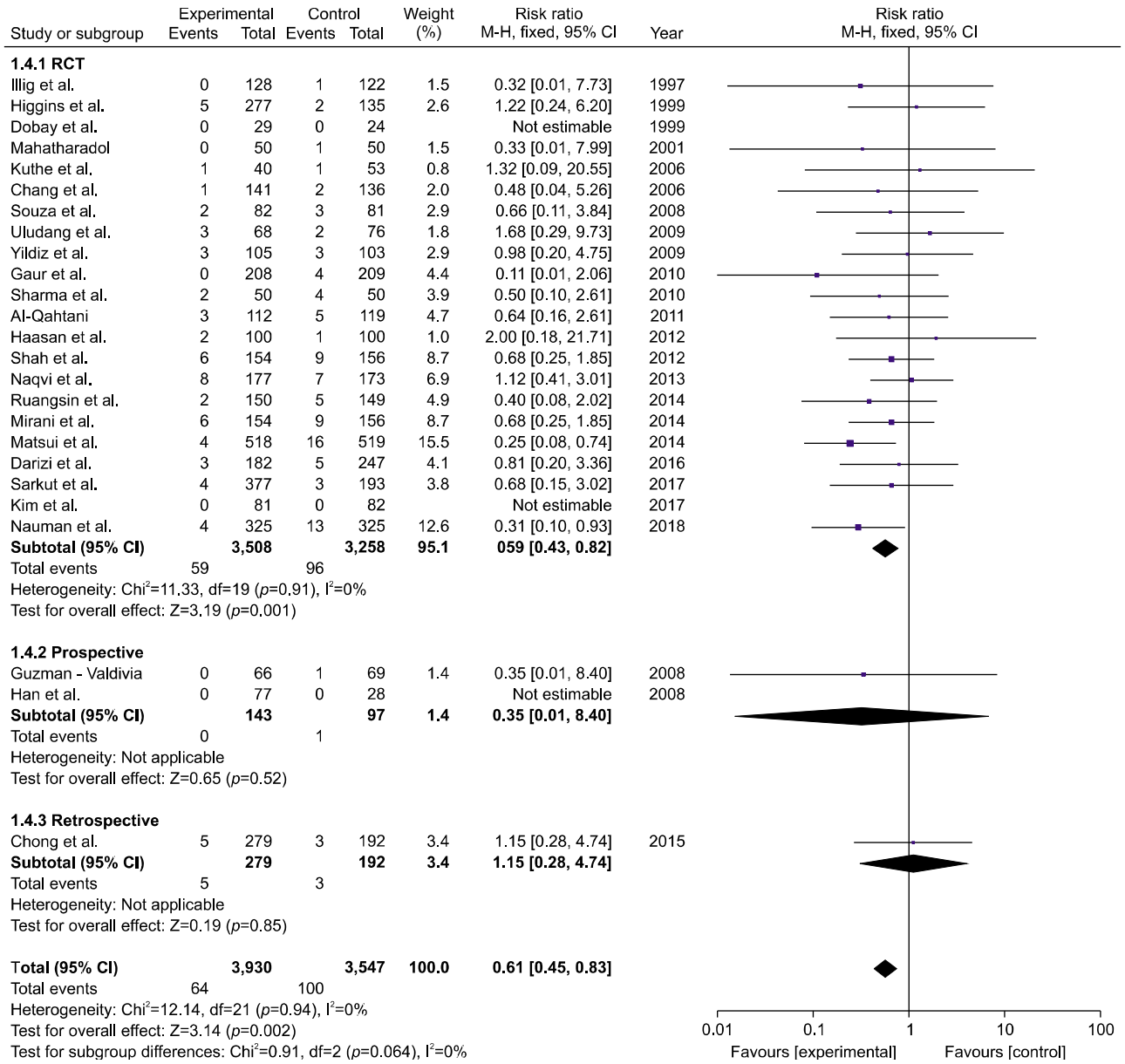

Fig. 3. Forest plot for superficial surgical site infections in low-risk patients undergoing elective laparoscopic cholecystectomy. A Mantel-Haenszel fixed-effect model was for used for meta-analysis. Risk ratios are shown 95% confidence intervals.

RCTs,[21,23,25,26,28-36,38,40,42,43,45,46] 2 prospective studies,[49,50] and one retrospective study.[52] In 19 RCTs, 10 (0.35%) of the 2890 patients in the prophylactic antibiotic group developed deep SSI compared with 10 (0.38%) of the 2637 patients in the no prophylaxis group. The prophylactic antibiotics did not reduce the incidence of deep SSI compared with control group (RR 1.01, 95% CI [0.46-2.21], p=0.98). No significant heterogeneity was found among included studies (p=0.77, I^2=0%). In 2 prospective studies, 0 (0.00%) of the 143 patients in the prophylactic antibiotic group developed deep SSI compared with 0 (0.00%) of the 97 patients in the no prophylaxis group. In a retrospective study, 0 (0.00%) of the 279 patients in the prophylactic antibiotic group developed SSI compared with 0 (0.00%) of the 192 patients in the no prophylaxis group. In the overall pooled event rate including 19 RCTs, 2 prospective studies, and one retrospective study, 10 (0.30%) of the 3312 patients in the prophylactic antibiotic group developed deep SSI compared with 10 (0.34%) of the 2926 in the no prophylaxis group. No difference was observed in outcomes between the two groups (RR 1.01, 95% CI [0.46-2.21], p=0.98) without significant heterogeneity among included studies (p=0.77, I^2=0%) (Fig. 4).

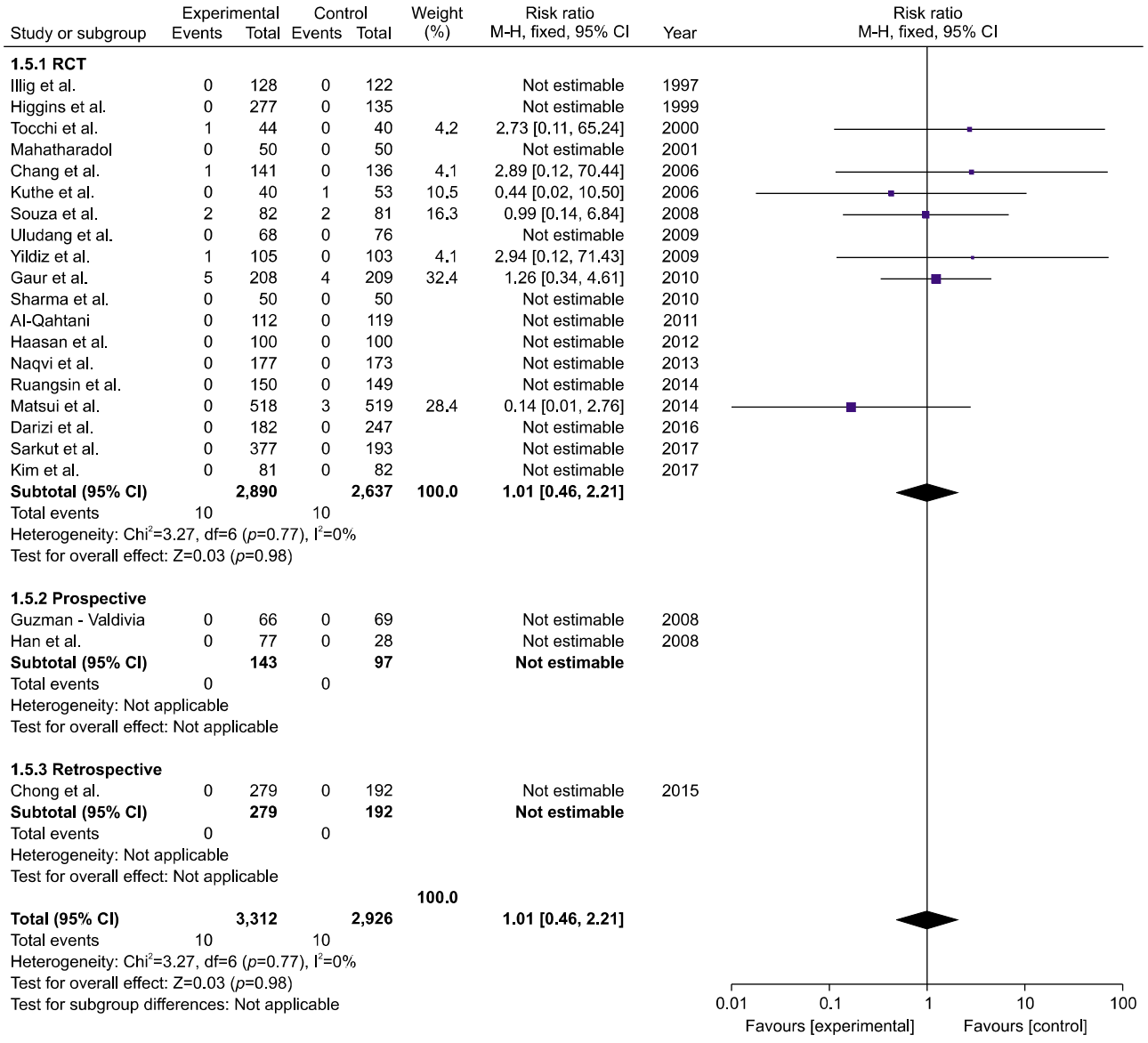

Fig. 4. Forest plot for deep surgical site infections in low-risk patients undergoing elective laparoscopic cholecystectomy. A Mantel-Haenszel fixed-effect model was for used for meta-analysis. Risk ratios are shown 95% confidence intervals.

Table 5. Sensitivity analyses

Subgroup	High-quality studies	Pooled effects	Heterogeneity
SSIs	25 RCTs[22-37,39-47] 2 Prospective studies[48,49]	RR 0.60, 95% CI [0.45-0.80] (p=0.0006)	I^2=0 (p=0.58)
Superficial SSI	19 RCTs[22,23,26,28,29,31-37,40-43,45-47] 1 Prospective study[49]	RR 0.54, 95% CI [0.38-0.77] (p=0.0007)	I^2=0 (p=0.89)
Deep SSI	10 RCTs[23,25,26,28,32-35,40,45] 1 Prospective study[49]	RR 1.10, 95% CI [0.45, 2.69] (p=0.84)	I^2=0 (p=0.57)

SSIs, surgical site infections; RCTs, randomized controlled trials; RR, risk ratio; CI, confidence interval.

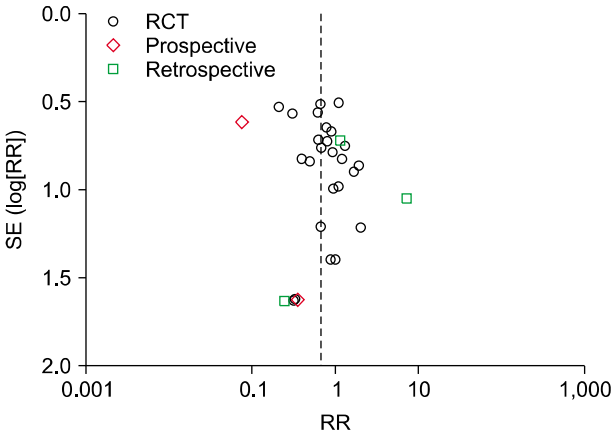

Fig. 5. Funnel plot for determination of publication bias in the subgroup analysis of SSI from all included studies. RR, Risk ratio; SE, Standard error.

Sensitivity test

Sensitivity tests were performed by excluding all low-quality studies including 3 RCTs[20,21,38] with Jadad score ≤2 and 4 non-randomized studies[22,50-52] with Newcastle-Ottawa Scale score ≤6. In these sensitivity tests of all subgroups, the results were similar to those of the primary meta-analyses in pooled effect size and heterogeneity. Table 5 shows all sensitivity tests of the subgroups. To determine the effect of individual study, sensitivity analysis excluding one study at a time was also performed. Removal of the largest study[48] including 2883 patients did not influenced the substantial change of the outcome (RR 0.74, 95% CI [0.56-0.97], p=0.03) in subgroup analysis of SSI.

Publication bias

A funnel plot of the included studies showed asymmetry, suggesting publication bias in the subgroup analysis of SSI (Fig. 5).

DISCUSSION

This systematic review and meta-analysis included a total of 12121 patients from the 7770 patients in 28 RCTs, 3123 patients in 3 prospective studies, and 1228 patients in 3 retrospective studies. This study concluded that the use of prophylactic antibiotics in low-risk patients undergoing elective laparoscopic cholecystectomy prevents SSI and superficial SSI other than deep SSI. Previous meta-analyses[3-13] were based only on data from RCTs and concluded that prophylactic antibiotics were not effective in preventing postoperative SSI in low-risk elective laparoscopic cholecystectomy, except for two studies.[10,12]

In previous several meta-analyses on this topic, only RCTs were included to determine the overall effect rate. Therefore, these meta-analyses were performed with relatively small sample sizes and were statistically under-powered. To overcome the limitation of the study including only RCTs with small sample sizes, this meta-analysis comprised a total of 12121 patients from both RCTs and non-RCTs to obtain appropriate statistical power in the subgroup analysis of SSI, superficial SSI, and deep SSI. Moreover, all available RCTs and non-RCTs that have not been published in English were used in this study to reduce language bias. Although there was a possibility of inducing significant heterogeneity by combining RCTs with non-RCTs, there were no significant differences in results between RCTs alone and RCTs and non-RCTs in all subgroup analyses.

This systematic review and meta-analysis has several limitations. First, of the 28 RCTs, 3 trials have low quality with Jadad score. In addition, of the 6 non-RCTs, 4 studies were of “low quality” assessed by the Newcastle-Ottawa Scale. Therefore, sensitivity test was performed to obtain pooled data rate. Second, there was significant het-

erogeneity among non-RCTs in subgroup analysis of SSI. Third, few RCTs provide the data regarding high-risk patients associated with diabetes mellitus, steroid or immunosuppressive therapy, biliary obstruction, jaundice, antibiotic intake 7 days prior to surgery, emergency cholecystectomy, acute or chronic cholecystitis 6 weeks before surgery, and open conversion surgery. Therefore, whether prophylactic antibiotics play a role in high-risk laparoscopic cholecystectomy still remains unclear. Fourth, the number of patients in the included studies is insufficient to avoid type II error because most of the trials, including RCTs and non-RCTs, in this meta-analysis showed a relatively low incidence rate of SSI and very low difference in incidence rate between the prophylactic antibiotic group and control group. Fifth, there was publication bias evaluated by funnel plot that showed asymmetry, which suggests that small sample size studies reporting negative results have not been published. Sixth, most of the included RCTs in this review were performed per-protocol analysis instead of intension-to-treat analysis, inducing misleading results.[85]

In addition, an important consideration of this meta-analysis is the inconsistency of the inclusion criteria in the included studies. The Scottish Intercollegiate Guidelines Network[1] and the American Society of Health-System Pharmacists guideline[2] suggest intraoperative gallbladder rupture, open conversion, acute cholecystitis, jaundice, immunosuppression, pregnancy and implantation of prosthetic devices as high-risk factors for SSI. The Scottish Intercollegiate Guidelines Network[1] also include diabetes, emergency surgery, long duration of procedures, ASA score of 3 or higher, recent episode of colic within 30 days before surgery and age ＞70 years as high-risk group for SSI. However, several studies[23,25-28,46] included patients with an ASA score of 3 or the ASA score was not applied to inclusion criteria in several RCTs.[22,32,38,40,43] Therefore, future studies need to provide a consistent set of inclusion criteria based on guidelines for defining low-risk or high-risk groups for SSI.

In conclusion, the overall pooled data of this meta-analysis from the present data including RCTs, prospective studies, and retrospective studies support the use of prophylactic antibiotics prior to elective laparoscopic cholecystectomy in low-risk patients to prevent SSIs and superficial SSIs. To assess the exact beneficial effects of antibiotic prophylaxis for laparoscopic cholecystectomy, more well-designed multicenter RCTs with large sample size, different population groups, and adequate statistical power for high-risk patients are necessary because most of the trials on this topic have focused on particularly the low-to-moderate risk patients. Furthermore, subgroup analyses including overall infection, extra-abdominal infection, and duration of postoperative hospital stay are also required with recent RCTs and non-RCTs.

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