#### **ORIGINAL PAPERS**

### Meta-analysis of the association between appendiceal orifice inflammation and appendectomy and ulcerative colitis

Peng Deng<sup>1</sup> and Junchao Wu<sup>2</sup>

Departments of <sup>1</sup>Emergency and <sup>2</sup>Digestive Internal Medicine. West China Hospital. Chengdu, China

#### ABSTRACT

**Objective:** This study aimed to investigate the relationship between appendiceal orifice inflammation (AOI) and appendectomy and ulcerative colitis (UC) by a meta-analysis.

**Methods:** Databases were thoroughly searched for studies on AOI and UC up to January 2016. Three comparisons were performed: a) whether the previous appendectomy was a risk factor of UC; b) influence of appendectomy on UC courses; c) influence of AOI on UC severity. Odds ratios (ORs) and 95% confidence intervals (CIs) were the effects sizes. The merging of results and publication bias assessment were performed by using RevMan 5.3. Sensitivity analysis was conducted using Stata 12.0.

**Results:** Nineteen studies were selected in the present study. Results of comparison I showed that appendectomy was a protective factor of UC (OR = 0.44; 95% CI [0.30, 0.64]). Comparison II indicated appendectomy had no significant influence in the courses of UC (proctitis: OR = 1.03, 95% CI [0.74, 1.42]; left-sided colitis: OR = 1.01, 95% CI [0.73, 1.39]; pancolitis: OR = 0.92, 95% CI [0.59, 1.43]; colectomy: OR = 1.38, 95% CI [0.62, 3.04]). Comparison III indicated UC combined with AOI did not affect the courses of UC (proctitis: OR = 1.15, 95% CI [0.67, 1.98]; left-sided colitis: OR = 1.14, 95% CI [0.24, 5.42]; colectomy: OR = 0.36, 95% CI [0.10, 1.23]). Sensitivity analysis confirmed the robust of the results in the present study.

**Conclusion:** In conclusion, this meta-analysis indicated appendectomy can reduce the risk of UC. But appendectomy or AOI had no influence on the severity of the disease and the effect of surgical treatment.

*Key words:* Appendiceal orifice. Punctiform erosion. Ulcerative colitis.

#### **INTRODUCTION**

Ulcerative colitis (UC) is one of the inflammatory bowel diseases (IBD), including UC and Crohn's disease (CD),

Acknowledgements: The authors thank West China Hospital for Excellent Technical Support.

*Received:* 20-12-2015 *Accepted:* 05-02-2016

e-mail: nojunchao@163.com

that affect 8 to 246 per 100,000 individuals (1,2). The classic characteristics are continuous and dispersive inflammation extending proximally from the rectum (3). The rectum, the rectosigmoid area, the left colon and the entire colon are common anatomic UC locations (4). It has been found that the number of patients with UC is on the rise year by year in our country, and UC contributes to developing cancers such as colorectal cancer (1). Extensive epidemiology studies on IBD have been conducted and its risk factors, such as familial aggregation, smoking habits and appendectomy, have been identified (5-7).

Cecal appendix has been repeatedly implicated in the pathogenesis and clinical course of UC (8). Appendectomy is strongly correlated with a decreased incidence of UC (9-12), indicating that appendicitis may have a relationship with UC. Furthermore, other studies showed that 71-88% of children with extensive UC had active inflammation in the appendiceal orifice (13,14). All these studies seem to draw attention to this skip-lesion change in UC. The clinical significance of appendiceal orifice inflammation (AOI) in UC has been extensively elucidated (15-17).

However, a different view supporting that AOI seems to have little prognostic implication for UC patients has been promoted (18). What is more, Ko et al. argue that appendectomy is a risk factor for UC among Middle Eastern migrants, while it is a protective factor among Caucasian populations (19). Besides, investigators have reported an inconsistent therapeutic effect on treating UC patients who were resistant to conventional medical therapy with appendectomy (20). Therefore, it is necessary to investigate whether AOI contributes to the development of UC.

In this study, we systematically retrieved the databases to identify the relevant studies. Then, we completed a meta-analysis with three comparisons to explore the relationship between AOI and UC.

DOI: 10.17235/reed.2016.4176/2015

*Correspondence:* Junchao Wu. Department of Digestive Internal Medicine. West China Hospital. Guoxue lane, 37. 610000 Wuhou District. Chengdu, China

Deng P, Wu J. Meta-analysis of the association between appendiceal orifice inflammation and appendectomy and ulcerative colitis. Rev Esp Enferm Dig 2016;108(7):401-410.

#### MATERIAL AND METHODS

This meta-analysis was presented in accordance with the guidelines of PRISMA.

#### Search strategy

PubMed, Embase and Cochrane Library bibliographic databases were thoroughly searched up to January 2016. Manual document tracing was also conducted for relevant studies. The key words were ulcerative colitis (UC), appendiceal orifice inflammation (AOI), and appendectomy. The search strategy was ((ulcerative colitis) OR UC) AND ((appendiceal orifice inflammation) OR appendectomy). There was no restriction on the language.

#### **Study selection**

Two investigators (A and B) independently selected the study according to the inclusion criteria. In case of disagreement, a third investigator (C) was induced for discussion. The inclusion criteria were as follows: a) studies related to appendicitis and ulcerative colitis; b) the subjects were adults; and c) studies contained at least one of the outcomes. The exclusion criteria were as follows: a) duplicates; and b) studies whose outcome measures could not be obtained.

In addition, manual searching of the printed literature, reference lists of reviews and included studies were also performed for obtaining more relevant studies for the meta-analysis.

#### Data extraction and quality estimation

Authors A and B independently extracted the data, including first author, publication year, study type, country, patients (including time, groups, number and age of the subjects), and outcomes. Any disagreement was resolved by discussion with author C. Newcastle-Ottawa Scale (NOS) (21) was used for quality assessment, which was conducted by author B and C.

#### Statistical analysis

There were three comparisons in this meta-analysis:

- Comparison I: UC patients vs. healthy control; outcome: previous appendectomy.
- Comparison II: UC patients under appendectomy vs. no appendectomy; outcomes: disease extent (proctitis, left-sided colitis, pancolitis), colectomy.
- Comparison III: UC patients AOI positive vs. AOI negative; outcomes: disease extent (proctitis, left-sided colitis), surgical therapy.

Odds ratios (ORs) and 95% confidence intervals (CIs) were used as effect sizes. Cochran's Q test and I<sup>2</sup> test (22) were used to assess heterogeneity among studies, with p < 0.05 or I<sup>2</sup> > 50% indicating significant heterogeneity, and the random effects model was used for data merge; otherwise the fixed effect model was used. Publication bias was assessed by the funnel plot. All the statistical analyses were performed by using RevMan 5.3 software (Nordic Cochrane Centre, Copenhagen, Denmark).

Sensitivity analysis was conducted by removing one study each time. Stata 12.0 software was used for this process.

#### RESULTS

#### Study selection

The procedures for the study selection are displayed in figure 1. We firstly found 639 studies (PubMed: 211; Embase: 424; Cochrane Library: 4). After removing 133 duplicates, 506 studies remained. Then, 321 completely unrelated studies and 140 reviews, letters or abstracts were excluded, and 45 articles remained. By screening of the full text, 19 studies were finally included in the present meta-analysis (5-7,15-17,19,23-34). The basic information of the selected studies is listed in tables I-III. All the studies had high quality with NOS 6-8.

## The results of comparison I: appendectomy was a protective factor of UC

Comparison I was conducted among 11 studies (5-7,19,25,27,28,30-32,34) with 10,889 subjects (UC patients: 4,673; healthy control: 6,216).



Fig. 1. Process of studies selection.

2016.	Vol.	108.	N.º 7
2010,	, 01.	100,	11. /

#### META-ANALYSIS OF THE ASSOCIATION BETWEEN APPENDICEAL ORIFICE INFLAMMATION AND APPENDECTOMY AND ULCERATIVE COLITIS

		lable I. Characteristics o	or the articles inclu	aea in comparison	I: UC patients vs	nealtny control		
Study	Country	Period of the participants included	Group	No. (MIF)	Age at diagnosis, y	Previous appendectomy	OR (95% CI)	Quality assessment
Castiglione,	,+I	1100/00 0100/00	NC	527 (285/242)	37 (16-63) <sup>1</sup>	49	0.28 (0.20, 0.40)	u
2012	Iraiy		Healthy control	562 (310/252)	39 (18-66)	149		D
			NC	294 (152/142)	$32.7 \pm 0.86^2$	19	0.26 (0.16, 0.43)	с
FIOLIII, 2004	Australia	AN	Healthy control	1,016 (551/465)	$33.6 \pm 0.38^2$	211		Ø
			NC	653 (328/325)	NA	NA	0.41 (0.27, 0.63)	С
deally, 2010	New Zealdin	CUU2/CU-CUU2/QU	Healthy control	600 (285/315)	NA	NA		o
			NC	148 (53/95)	34 (14-73)	10	0.96 (0.45, 2.04)	٢
riavaly, zulo	DVdKId	2000-20002	Healthy control	355 (167/188)	28 (16-81)	25		_
			MEM-UC	79 (35/44)	42.5		5.00 (1.59, 15.70)	
	()               		MEM-control	153 (76/77)	37.1			с
C107 '0V	Ausualia	-0007	Caucasian-UC	77 (40/37)	49.1	<b>Y</b> N	0.47 (0.17-1.29)	Ø
			Caucasian-control	173 (83/90)	44.9			
López-Serrano,			NC	146 (60/86)	49.7 ± 16.6 <sup>3</sup>	6	0.44 (0.21, 0.94)	Ĺ
2010	Ulbdc	2004-	UC-control	278 (NA)	NA	36		٥
Naganuma,	2		NC	325 (170/155)	38.9 ± 13.7 <sup>3</sup>	21	0.35 (0.21, 0.60)	с
2001	Japan	0007/20-2221/20	UC-control	325 (170/155)	39.3 ± 14.2	53		Ø
Radford-Smith,		1000	NC	307 (157/150)	$32.7 \pm 0.85^2$	21	0.24 (0.15, 0.39)	٢
2002	Australia	2221 -C221	UC-control	1,016 (551/465)	$33.6 \pm 0.38^2$	206		_
			NC	259 (133/126)	$43.1 \pm 0.89^2$	20	0.25 (0.15, 0.43)	٢
seiby, zuuz	Australia		Control	280 (134/146)	$41.1 \pm 0.82^2$	70		_
			NC	150 (NA)	NA	12	0.20 (0.10, 0.40)	9
	rencu	AN	Control	150 (NA)	NA	46		
			NC	1,308 (721/587)	$41.6 \pm 12.3^3$	44	1.05 (0.68, 1.61)	٢
vvalig, zuij		04/2001-04/2010	Control	1,308 (721/587)	$41.4 \pm 13.5^3$	42		/
UC: Ulcerative colitis mean ± SD.	;; M: Male; F: Female,	: y: Year; NA: Not available; OR: Od	ds ratio; Cl: Confidence i	nterval. <sup>1</sup> Data were prese	ented as median (rang	e); <sup>2</sup> Data were presente	d as mean ± SEM; ³Data v	vere presented as

~
Σ.
E
5
a
ğ
e L
ğ
ap
0
č
Š
5
Ê
ō
せ
e e
Ĕ
e
d
a.
er
þ
h
5
nt
ē
ati,
ă
U
Э
Ĭ
_
c
no
rison
arison
nparison
omparison
comparison
in comparison
is in comparison
les in comparison
ticles in comparison
articles in comparison
d articles in comparison
led articles in comparison
uded articles in comparison
cluded articles in comparison
included articles in comparison
e included articles in comparison
the included articles in comparison
f the included articles in comparison
of the included articles in comparison
cs of the included articles in comparison
tics of the included articles in comparison
ristics of the included articles in comparison
teristics of the included articles in comparison
icteristics of the included articles in comparison
iracteristics of the included articles in comparison
haracteristics of the included articles in comparison
Characteristics of the included articles in comparison
II. Characteristics of the included articles in comparison
e II. Characteristics of the included articles in comparison
ble II. Characteristics of the included articles in comparison
Table II. Characteristics of the included articles in comparison

				-	-	-	•		•		
Study	Country	Period of the participants included	Group	No. (MIF)	Age at diagnosis, y	Duration of symptoms	Proctitis	Left sided colitis	Pancolitis	Colectomy	Quality assessment
			App (before)	49 (13/26)	35.7 ± 15.6 <sup>1</sup>	$10.1 \pm 8.1 \text{ y}^1$	ß	13	19	∞	c
CUSHES, ZUUZ	LIGIICE	0007/71-1661/10	No App	589 (285/304)	32.9 ± 14.4	7.2 ± 8.3 y	70	168	239	194	0
			App (after)	202 (84/118)	38.6 ± 18.0					6	٢
Halids, 2004	Denmark	911/19/19/19/19	No App	808 (336/472)	38.7 ± 17.7		ı			42	~
			App (before)	68 (23/45)	41 (18-68) <sup>2</sup>	3 (0-83) m <sup>2</sup>	30	14		9	
Lee, 2015	Korea	07/1989-12/2013	App (after)	36 (19/17)	35 (11-73)	5 (0-61) m	15	12			00
			No App	2,544 (1,381/1,263)	36 (11-80)	3 (0-370) m	1,043	677	·	207	
Naganuma,			App (before)	21		12.1 ± 12.3 y	Ø	Ŀ	00		с
2001	Japan	0007/20-222100	No App	304		9.9 ± 7.8 y	55	93	156	·	o
Picazo-			App (after+ before)	38			ı			16	7
Ferrera, 2011	lilledc		No App	76						12	
			App (before)	12	$62.6 \pm 4.52^3$		-	ъ	ß	2	
Selby, 2002	Australia	NA	App (after)	Ø	53.8 ± 7.15	NA	-	ъ	-	-	7
			No App	239	$41.8 \pm 0.85$		80	69	50	21	
App: Appendecto presented as mear	my; UC: Ulcer i ± SEM.	ative colitis; M: Male; F: F	-emale; y: Year; m: Mont	hs; NA: Not available; App:	: Appendicitis. <sup>1</sup> Dat	a were presented as	s mean ± SD	; <sup>2</sup> Data wei	e presented a	s median (rang	e); <sup>3</sup> Data were

l. Characteristics of the included articles in comparison III (UC patients AOI positive vs AOI negative)	d of the Left Surgical Quality cipants Group No. (MIF) Age, y Duration of Follow-up, Proctitis sided Surgical Quality luded m colitis therapy assessment	AOI-positive 48 (19/29) 39 (17-71) <sup>1</sup> 5.5 (1-72) <sup>1</sup> 45 (12-85) 38 10 0 7	Adl-negative 46 (23/23) 45 (20-70) 7.5 (1-108) 41 (12-91) 30 16 1	UC-AOI 14 (11/3) 40 (19-61) <sup>1</sup> NA 78 (12-300) 11 NA 0	VA UC-control 25 (10/15) 40 (21-69) NA 96 (17-204) 21 NA 1 °	Appendicitis 7 34.7 <sup>2</sup> 72 <sup>2</sup> NA 1 NA NA 5	v-us/1990 No appendicitis 17 39.2 79 NA 0 NA NA O	Appendicitis 54 (32/22) 37.0 ± 11.7 <sup>2</sup> 91.0 ± 6.2 <sup>2</sup> NA 8 25 2	+-12/2000 No appendicitis 225 (134/91) 43.1 ± 13.5 87.8 ± 7.2 NA 43 59 23
Table III. Characteristics of the included article	Period of the participants Group No. (MI included	AOI-positive 48 (19/2	AOI-negative 46 (23/2	UC-AOI 14 (11/3	UC-control 25 (10/1	Appendicitis 7	No appendicitis	Appendicitis 54 (32/2	01/1994-12/2000 No appendicitis 225 (134/
	Study Country		byeon, zuuz			W. Brian,	1999 1999	Yamagishi,	2002 2002

404

There was significant heterogeneity ( $I^2 = 82\%$ , p < 0.0001) among studies, thus the random effects model was chosen. The merged OR was 0.44 (95% CI [0.30, 0.64], p < 0.0001) (Fig. 2A), indicating that appendectomy was a protective factor against UC.

# The results of comparison II: appendectomy did not affect the severity of UC

We further conducted comparison II to investigate the effects of appendectomy on the UC clinical course.



Fig. 2. Results for comparison I. A. Forest plot (a: Middle Eastern migrants; b: Caucasian subjects). B. Funnel plot.

Six studies (23,24,26,28,31,33) were involved in comparison II with 4,994 subjects (appendectomy: 434; no appendectomy: 4,560). These results were displayed in figure 3. There was no significant heterogeneity among studies on other outcomes of disease severity (proctitis, left sided colitis, pancolitis), excepting colectomy ( $I^2 =$ 72%, p = 0.003). No significant differences were found in disease courses between UC patients with appendectomy and those without appendectomy (proctitis: OR = 1.03, 95% CI [0.74, 1.42], p = 0.87; left sided colitis: OR = 1.01, 95% CI [0.73, 1.39], p = 0.97; pancolitis: OR = 0.92, 95% CI [0.59, 1.43], p = 0.70; colectomy: OR = 1.38, 95% CI [0.62, 3.04], p = 0.43). This fact indicated that appendectomy did not affect the severity of UC.

Besides, subgroup analysis by the different time for appendectomy was performed (Table IV).

A         appendectomy         no appendectomy         Odds Ratio         Odds Ratio           Study or Subprop         Formation         Total         Work         M.H. Fixed, 95% CL         M.H. Fixed, 95% CL           Connes 2002         5         49         70         689         13.2%         0.84 (0.32, 2.20)           Lee 2015         30         68         104.3         2544         41.6%         1.14 (0.70, 1.85)           Nagaruma 2001         8         21         65         304         66.9         2.78 (1.10, 70, 1.85)           Selby 2002         1         8         80         239         6.6%         0.28 (0.02, 2.35)           Selby 2002         1         12         80         239         6.6%         0.18 (0.02, 1.42]           Total (95% CL)         194         6459         100.0%         1.03 (0.74, 1.42]         1.00           Hetrospeneity: ChP = 8.92, df = 5 (P = 0.11); P = 44%         Test for overall effect 2 = 0.16 (P = 0.87)         Total (95% CL)         M-H. Fixed, 95% CL         M-H. Fixed, 95% CL           Coanse 2002         13         49         168         589         2.55.%         0.90 (0.47, 1.75)           Lee 2015         12         69         239         5.2%         0.71 (0.2								
Study or Subgroup         Events         Total         Weight         M-H. Fixed. 95% CI         M-H. Fixed. 95% CI           Consers 2002         5         49         70         599         32%         0.44         0.52, 2.03           Lee 2015         15         36         1043         2544         23.3%         1.03 [0.53, 2.00]           Lee 2015         30         68         1043         2544         423.3%         1.03 [0.53, 2.00]           Selby 2002         1         12         80         239         6.6%         0.18 [0.02, 1.42]           Total (95% CI)         194         6459         100.0%         1.03 [0.74, 1.42]         10           Total (95% CI)         194         6459         100.0%         1.03 [0.74, 1.42]         10           Study or Subgroup         Events         Total         Yeints         Total Weight         M-H. Fixed. 95% CI         M-H. Fixed. 95% CI           Lee 2015         12         36         677         2544         17.08         130 [0.69, 277]         M-H. Fixed. 95% CI           Lee 2015         12         86         677         2544         17.08         130 [0.69, 277]         M-H. Fixed. 95% CI           Study or Subgroup         Events	А	appendec	tomy	no appende	ectomy		Odds Ratio	Odds Ratio
Conses 2002 5 49 70 589 13.2% 0.44 [0.32, 2.20] Lee 2015 16 36 1043 2544 41.6% 1.14 [0.70, 1.86] Naganuma 2001 8 21 55 304 6.0% 2.79 [1.0, 7.06] Setby 2002 1 8 80 239 6.2% 0.28 [0.03, 2.36] Fall (9% C) 194 6459 100.0% 1.03 [0.74, 1.42] Total events 60 2371 Heterogeneity: ChP = 8.92, dF 5P 0.11); P = 44% Total organized effect 2 = 0.16 (P = 0.87) B Study or Subgroup Events Total Events Total Weight M-H. Exact, 95% Cl 0.02 (0.4, 1.75] Lee 2015 14 68 66 77 2544 17.0% 0.00 (0.47, 1.76] Study or Subgroup Events Total Events Total Weight M-H. Exact, 95% Cl 0.00 (0.47, 1.76] Setby 2002 5 8 69 225 % 0.00 (0.47, 1.76] Study or Subgroup Events Total Events Total Weight M-H. Exact, 95% Cl 0.02 (0.4, 1.76] Study or Subgroup Events Total Events Total Weight M-H. Exact, 95% Cl 0.00 (0.47, 1.76] Study or Subgroup Events Total Events Total Weight M-H. Exact, 95% Cl 0.00 (0.47, 1.76] Study or Subgroup Events Total Events Total Weight M-H. Exact, 95% Cl 0.00 (0.47, 1.76] Study or Subgroup Events Total Events Total Weight M-H. Exact, 95% Cl 0.00 (0.47, 1.76] Total (95% Cl) 194 6459 100.0% 0.71 (0.25, 1.99] C appendectomy no appendectomy Odds Ratio Odds Ratio Odds Ratio Corres 2002 15 8 69 239 5.2% 1.76 (0.54, 5.73] C appendectomy no appendectomy Events Total Events Total Weight M-H. Exact, 95% Cl 0.00 (0.47, 1.76] Study or Subgroup Events Total Events Total Weight M-H. Exact, 95% Cl 0.00 (0.47, 1.76] Study or Subgroup Events Total Events Total Weight M-H. Exact, 95% Cl 0.00 (0.46, 4.68] Setby 2002 5 12 50 239 6.9% 2.70 (0.82, 8.87] Total events 43 495 100.0% 0.92 (0.59, 1.43] Total events 43 495 100.0% 0.92 (0.59, 1.43] Total events 43 495 100.0% 0.92 (0.59, 1.43] Total events 43 14 16 89 20.7 2544 100 (0.46, 8.46] Heterogeneity: ChP = 4.30, dF = 3 (P = 0.23); P = 31% Test for overall effect Z = 0.36 (P = 0.70) Favours [appendectomy] Evours [no appendectomy] Evours [no appendectomy] Favours [no appendectomy] Evours [no appendectomy] D 0.5 0.2 1 5 20 Favours [appendectomy] Evours [no appende	Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% CI
Lee 2015 15 30 68 1043 2544 423.3% 1.03 [0.53, 2.00] Nagaruma 2001 8 21 55 304 6.0% 2.79 [1.10, 7.0.5] Selby 2002 1 8 21 55 304 6.0% 2.79 [1.10, 7.0.5] Selby 2002 1 8 22 45 62% 0.28 [0.0.3, 2.5] Selby 2002 1 1 12 80 239 9.6% 0.18 [0.02, 1.42] Total (95% CI) 194 6459 100.0% 1.03 [0.74, 1.42] Total events 8 60 239 6.5% 0.18 [0.04, 7, 1.75] B appendectomy no appendectomy Odds Ratio Odds Ratio MH. Fixed, 95% CI Consec 2002 5 8 69 239 2.3% 4.11 [0.94, 1.76] Selby 2002 5 8 69 239 2.3% 4.11 [0.94, 1.76] Total events 50 172 544 7.7% 0.71 [0.94, 1.59] Total events 50 172 544 7.7% 0.71 [0.94, 1.59] Selby 2002 5 8 69 239 2.3% 4.11 [0.96, 1.7.6] Total (95% CI) 194 6459 100.0% 1.01 [0.73, 1.39] Total events 50 175 349 Selby 2002 5 8 69 239 2.3% 4.11 [0.96, 1.7.6] Total (95% CI) 194 6459 100.0% 1.01 [0.73, 1.39] Total events 51 12 36 697 2544 7.7% 0.71 [0.54, 1.59] Total events 52 172 69 239 5.2% 1.76 [0.94, 5.73] Total events 52 175 349 Selby 2002 5 8 69 239 2.3% 4.11 [0.96, 1.7.6] Total (95% CI) 194 6459 100.0% 1.01 [0.73, 1.39] Total events 54 1753 Total events 54 1753 Total events 54 1753 Total events 53 12 69 239 5.2% 1.76 [0.94, 1.75] Total (95% CI) 194 6459 100.0% 0.92 [0.51, 1.69] MH. Fixed, 95% CI Consec 2002 19 49 239 589 55.4% 0.93 [0.51, 1.69] MH. Fixed, 95% CI Consec 2002 19 49 239 589 55.4% 0.93 [0.51, 1.69] MH. Fixed, 95% CI Consec 2002 19 49 239 589 55.4% 0.93 [0.51, 1.69] MH. Fixed, 95% CI Consec 2002 19 49 239 598 55.4% 0.93 [0.51, 1.69] MH. Fixed, 95% CI Consec 2002 19 49 239 598 55.4% 0.93 [0.51, 1.69] MH. Fixed, 95% CI Consec 2002 19 49 239 598 55.4% 0.93 [0.51, 1.69] MH. Fixed, 95% CI Consec 2002 19 49 239 242 808 20.5% 0.93 [0.42, 1.47] Total events 33 Hais 200 49 212 24 28 08 20.5% 0.93 [0.42, 0.87] Favours [appendectom] Favours [no appendectom] Favours [appendectom]	Cosnes 2002	5	49	70	589	13.2%	0.84 [0.32, 2.20]	
Lee 2015 30 66 1043 2544 41.6% 1.14 [0.70, 1.85] Selby 2002 1 8 21 55 304 6.0% 2.79 [1.10, 7.05] Selby 2002 1 8 20 2.99 9.6% 0.18 [0.02, 1.42] Total (9% C) 194 645 100.0% 1.03 [0.74, 1.42] Total events $60$ 2371 Helerogeneity: Ch <sup>2</sup> = 2.0.16 (P = 0.37) B appendectomy no appendectomy odds Ratio Study or Subproup Events Total Fixed 55% CI Coarnes 2002 13 49 168 589 25.5% 0.90 [0.47, 1.75] Lee 2015 14 66 677 2544 7.7% 0.71 [0.25, 1.99] Selby 2002 5 8 69 239 2.5% 0.90 [0.47, 1.55] Total (95% CI) 194 6459 100.0% 1.38 [0.69, 2.77] Lee 2015 14 66 677 2544 7.7% 0.71 [0.25, 1.99] Selby 2002 5 8 69 239 2.5% 0.77 [0.54, 6.73] Selby 2002 5 8 69 239 2.5% 0.71 [0.54, 6.73] Total (95% CI) 194 6459 100.0% 1.01 [0.73, 1.39] C appendectomy no appendectomy odds Ratio Odds Rati	Lee 2015	15	36	1043	2544	23.3%	1.03 [0.53, 2.00]	
Nagaruma 2001       8       21       55       304       6.0%       2.79 [1.10, 7.65]         Selby 2002       1       12       80       239       9.6%       0.18 [0.02, 1.42]         Total (95% CI)       194       6459       100.0%       1.03 [0.74, 1.42]         Test for cveral effect: Z = 0.16 (P = 0.87)       rotal events       60       2371         B       appendectomy       no appendectomy       Odds Ratio         Study or Subgroup       Events       Total       Weight       M-H. Fixed, 95% CI       M-H. Fixed, 95% CI         Conses 2002       13       49       168       559       25.5%       0.90 [0.47, 1.75]       0.00 [0.47, 1.75]         Lee 2015       12       68       677       2544       37.7%       0.71 [0.25, 1.99]       0.41 [0.5%, CI]       0.44 (F stod, 95% CI         Nagaruma 2001       5       12       69       239       5.3%       1.76 [0.54, 5.73]       0.90 [0.47, 1.75]         Selby 2002       5       8       69       239       5.55 4%       0.90 [0.47, 1.75]       0.90 [0.46 Ratio         Conses 2002       19       49       239       558 5.54%       0.93 [0.51, 1.69]       0.56 [0.2 (C)       0.5 [0.2 (C)       0.5 [0.2 (C)       <	Lee 2015	30	68	1043	2544	41.6%	1.14 [0.70, 1.85]	
Selby 2002 1 8 8 00 239 9.6% 0.28 (0.3, 2.85) Selby 2002 1 12 80 239 9.6% 0.18 [0.02, 1.42] Total (9%, CI) 194 6459 100.0% 1.03 [0.74, 1.42] Heterogeneity: Ch <sup>P</sup> = 6.92, df = 5 (P = 0.11); P = 44% Test for vortrail effect: Z = 0.16 (P = 0.87) B appendectomy no appendectomy Study or Subgroup Events Total Vents Total Vents Total Weight M-H. Fixed. 95% CI Cosnes 2002 15 12 36 677 2544 17.0% 1.38 [0.89, 2.77] Lee 2015 12 36 677 2544 17.0% 1.38 [0.89, 2.77] Lee 2015 14 68 677 2544 17.0% 1.38 [0.89, 2.77] Lee 2015 12 36 677 2544 17.0% 1.38 [0.89, 2.77] Lee 2015 12 93 304 12.3% 0.71 [0.25, 1.99] Selby 2002 5 8 69 239 2.3% 4.11 [0.96, 17.65] Total (95% CI) 194 6459 100.0% 1.01 [0.73, 1.39] Total (95% CI) 194 6459 100.0% 1.01 [0.73, 1.39] C appendectomy no appendectomy of the C = 0.22); P = 23% Total (95% CI) 19 49 238 569 55.4% 0.76 [0.54, 57.3] C appendectomy no appendectomy of the C = 0.22); P = 23% Total (95% CI) 19 49 239 569 55.4% 0.53 [0.24, 1.46] C appendectomy no appendectomy of the C = 0.22); P = 23% Total (95% CI) 19 49 239 7.0% 0.54 [0.66, 4.49] Selby 2002 5 12 50 239 6.9% 2.70 [0.82, 8.67] Total (95% CI) 9 0 1371 100.0% 0.92 [0.59, 1.43] Total (95% CI) 9 0 1371 100.0% 0.92 [0.59, 1.43] Total (95% CI) 9 0 1371 100.0% 0.92 [0.59, 1.43] Total (95% CI) 9 0 1371 100.0% 0.92 [0.59, 1.43] Total (95% CI) 9 0 1371 100.0% 0.92 [0.59, 1.43] Total (95% CI) 9 0 1371 100.0% 0.92 [0.59, 1.43] Total (95% CI) 9 0 1371 100.0% 0.92 [0.59, 1.43] Total (95% CI) 9 0 1371 100.0% 0.92 [0.59, 1.43] Total (95% CI) 9 0 1371 100.0% 0.92 [0.59, 1.43] Total (95% CI) 9 0 1371 100.0% 0.92 [0.59, 1.43] Total (95% CI) 9 14 6 21 229 8.8% 1.48 [0.17, 1.264] Pietrogramma 16fetz Z = 0.36; Ch <sup>P</sup> = 0.02); P = 72% D Genes 2002 1 8 49 194 589 20.1% 0.40 [0.16, 0.66] Helles 20.65; Ch <sup>P</sup> = 18.05; Ch <sup>P</sup> = 18.0	Naganuma 2001	8	21	55	304	6.0%	2.79 [1.10, 7.05]	
Selby 2002       1       12       80       239       9.6%       0.18 [0.02, 1.42]         Total (95% CI)       194       6459       100.0%       1.03 [0.74, 1.42]         Heterogeneity: ChiP = 8.92, df = 5 (P = 0.11); P = 44%       100       500       2371         Heterogeneity: ChiP = 8.92, df = 5 (P = 0.11); P = 44%       100       500       Favours [appendectomy]       Favours [appendectomy]         Study or Subgroup       Events       Total       Weight       M-H. Eixed, 95% CI       M-H. Fixed, 95% CI         Conses 2002       13       49       168       559       25.5%       0.90 [0.47, 1.75]       Favours [appendectomy]       Favours [appendectomy]         Lee 2015       12       66       677       2544       37.7%       0.71 [0.25, 1.99]         Lee 2015       14       68       677       2544       37.7%       0.71 [0.25, 1.99]         Selby 2002       5       8       69       239       2.3%       1.16 [0.96, 17.65]         Total (95% CI)       194       6459       100.0%       1.01 [0.73, 1.39]       0.05       0.2       1.5       20         Selby 2002       5       12       50       239       5.8%       0.93 [0.51, 1.69]       0.05       0.2	Selby 2002	1	8	80	239	6.2%	0.28 [0.03, 2.35]	
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $	Selby 2002	1	12	80	239	9.6%	0.18 [0.02, 1.42]	
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $	Total (95% CI)		194		6459	100.0%	1.03 [0.74, 1.42]	•
Heterogeneity: Chi <sup>2</sup> = 8.92, df = 5 (P = 0.11); P = 44% Test for overall effect: Z = 0.16 (P = 0.87) B appendectomy no appendectomy odds Ratio Study or Subgroup Events Total Events Total Weight M-H. Fixed, 95% CI Cosnes 2002 13 49 168 599 25.5% 0.90 (0.47, 1.76) Lee 2015 12 36 677 2544 17.0% 0.71 (0.28, 1.99) Solty 2002 5 12 69 239 5.2% 1.76 (0.54, 5.73) Solty 2002 5 12 69 239 5.2% 1.76 (0.54, 5.73) Solty 2002 5 18 69 239 5.2% 1.76 (0.54, 5.73) Solty 2002 5 18 69 239 2.3% 4.11 (0.96, 17.65] Total (95% CI) 194 6459 100.0% 1.01 [0.73, 1.39] C cosnes 2002 19 49 239 589 55.4% 0.93 (0.51, 1.69) Naganuma 2001 8 21 156 304 30.8% 0.38 (0.51, 1.69) Naganuma 2001 8 21 156 304 30.8% 0.38 (0.51, 1.69) Naganuma 2001 8 21 156 304 30.8% 0.38 (0.51, 1.69) Naganuma 2001 8 21 156 304 30.8% 0.38 (0.51, 1.69) Naganuma 2001 8 21 156 304 30.8% 0.38 (0.51, 1.69) Naganuma 2001 8 21 156 304 30.8% 0.38 (0.51, 1.69) Naganuma 2001 8 21 156 304 30.8% 0.38 (0.51, 1.69) Naganuma 2001 8 21 156 304 30.8% 0.38 (0.51, 1.69) Naganuma 2001 8 21 156 304 30.8% 0.38 (0.51, 1.69) Naganuma 2001 8 21 156 304 30.8% 0.38 (0.54, 1.46) Sudy or Subgroup Events Total Events Total Weight M-H. Fixed, 95% CI Cosnes 2002 19 49 202 39 8.9% 5.7% 0.99 (0.44, 48] Selby 2002 5 12 2 0.23; P = 31% Total events 33 495 Heterogeneity: Chi <sup>2</sup> = 3.08 (P = 0.72); P = 31% Total events 33 495 Heterogeneity: Chi <sup>2</sup> = 3.08 (P = 0.72); P = 31% Total events Total Weight M-H. Random, 95% CI Cosnes 2002 8 40 9 202 42 808 20.5% 0.85 (0.41, 1.78) Heterogeneity: Chi <sup>2</sup> = 4.36, Chi <sup>2</sup> = 1.80, 5, df = 5 (P = 0.003); P = 72% Total (95% CI) 30 6 31 (1.77, 1.64) Haltas 2004 9 202 42 12 229 8.8% 1.48 (0.17, 12.64) Heterogeneity: Tai <sup>2</sup> = 0.65; Chi <sup>2</sup> = 1.80, 5, df = 5 (P = 0.003); P = 72% Total events 42 Heterogeneity: Tai <sup>2</sup> = 0.65; Chi <sup>2</sup> = 1.80, 5, df = 5 (P = 0.003); P = 72% Heterogeneity: Tai <sup>2</sup> = 0.65; Chi <sup>2</sup> = 1.80, 5, df = 5 (P = 0.003); P = 72% Heterogeneity: Tai <sup>2</sup> = 0.55; Chi <sup>2</sup> = 1.80, 5, df = 5 (P = 0.003); P = 72% Heterogeneity: Tai <sup>2</sup> =	Total events	60		2371				
Test for overall effect: Z = 0.16 (P = 0.87)       0.02       0.1       1       10       50         B       appendectomy       no appendectomy       Odds Ratio       Odds Ratio         Conses 2002       13       49       168       599       25.5%       0.90 (0.47, 1.75)         Lee 2015       12       36       677       2544       17.7%       1.38 (0.69, 2.77)         Lee 2015       14       68       697       2544       37.7%       0.71 (0.39, 1.30)         Naganuma 2001       5       21       93       304       12.2%       0.71 (0.25, 1.99)         Setby 2002       5       12       69       239       5.2%       1.76 (0.54, 5.73)         Setby 2002       5       8       69       239       5.2%       1.76 (0.54, 5.73)         Total (95% CI)       194       6459       100.0%       1.01 (0.73, 1.39)         Consec 2002       19       49       239       5.9% 5.0%       Odds Ratio         Study or Subgroup       Events       Total       Weight       M+H, Fixed, 95% CI         Consec 2002       19       49       239       5.9% 0.2% 0.55 (0.64, 4.99)         Naganuma 2001       8       50       239	Heterogeneity: Chi <sup>2</sup> =	8.92. df = 5 (	$P = 0.1^{\circ}$	); $ ^2 = 44\%$				
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $	Test for overall effect:	Z = 0.16 (P	= 0.87)	,,				0.02 0.1 1 10 50
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $	D		,					Favours [appendectomy] Favours [no appendectomy]
	D	appendec	tomy	no appende	ectomy		Odds Ratio	Odds Ratio
$ \begin{array}{c} \mbox{Cosnes 2002} & 13 & 49 & 168 & 589 & 25.5\% & 0.90 [0.47, 1.75] \\ \mbox{Lee 2015} & 12 & 36 & 677 & 2544 & 17.0\% & 1.38 [0.69, 2.77] \\ \mbox{Lee 2015} & 14 & 68 & 677 & 2544 & 17.0\% & 0.71 [0.25, 1.99] \\ \mbox{Naganuma 2001} & 5 & 21 & 93 & 304 & 12.3\% & 0.71 [0.25, 1.99] \\ \mbox{Selby 2002} & 5 & 12 & 69 & 239 & 2.3\% & 4.11 [0.96, 17.65] \\ \mbox{Total (95\% CI)} & 194 & 6459 & 100.0\% & 1.01 [0.73, 1.39] \\ \mbox{Total reducts} & 54 & 1753 \\ Heterogeneity: Ch2 = 7.02, df = 5 (P = 0.22); P = 29\% \\ \mbox{Test for overall effect: Z = 0.04 (P = 0.27); P = 29\% \\ \mbox{Test for overall effect: Z = 0.04 (P = 0.27); P = 29\% \\ \mbox{Test for overall effect: Z = 0.04 (P = 0.27); P = 29\% \\ \mbox{Test for overall effect: Z = 0.04 (P = 0.27); P = 29\% \\ \mbox{Test for overall effect: Z = 0.04 (P = 0.27); P = 29\% \\ \mbox{Test for overall effect: Z = 0.04 (P = 0.27); P = 29\% \\ \mbox{Test for overall effect: Z = 0.04 (P = 0.27); P = 29\% \\ \mbox{Test for overall effect: Z = 0.04 (P = 0.27); P = 21\% \\ \mbox{Test for overall effect: Z = 0.38 (P = 0.03); P = 31\% \\ \mbox{Test for overall effect: Z = 0.38 (P = 0.03); P = 31\% \\ \mbox{Test for overall effect: Z = 0.38 (P = 0.03); P = 31\% \\ \mbox{Test for overall effect: Z = 0.38 (P = 0.03); P = 72\% \\ \mbox{Test for overall effect: Z = 0.38 (P = 0.03); P = 72\% \\ \mbox{Test for overall effect: Z = 0.85 (Ch2 = 4.95 (D = 0.03); P = 72\% \\ \mbox{Test for overall effect: Z = 0.85 (Ch2 = 1.65, df = 5 (P = 0.03); P = 72\% \\ \mbox{Test for overall effect: Z = 0.85 (Ch2 = 1.65, df = 5 (P = 0.03); P = 72\% \\ \mbox{Test for overall effect: Z = 0.70 (P = 0.43) \\ \mbox{Test for overall effect: Z = 0.70 (P = 0.43) \\ \mbox{Test for overall effect: Z = 0.70 (P = 0.43) \\ \mbox{Test for overall effect: Z = 0.70 (P = 0.43) \\ \mbox{Test for overall effect: Z = 0.70 (P = 0.43) \\ \mbox{Test for overall effect: Z = 0.70 (P = 0.43) \\ \mbox{Test for overall effect: Z = 0.70 (P = 0.43) \\ \mbox{Test for overall effect: Z = 0.70 (P = 0.43) \\ \mbox{Test for overall effect: Z = 0.70 (P = 0.43) $	Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Lee 2015 12 36 677 2544 17.0% 1.38 [0.69, 2.71] Lee 2015 14 68 677 2544 37.7% 0.71 [0.39, 1.30] Naganuma 2001 5 21 93 304 12.3% 0.71 [0.25, 1.99] Selby 2002 5 12 69 239 5.2% 1.76 [0.54, 5.73] Selby 2002 5 8 69 239 2.3% 4.11 [0.96, 17.65] Total (95% Cl) 194 6459 100.0% 1.01 [0.73, 1.39] Total events 54 1753 Heterogeneity: Ch <sup>2</sup> = 3.6, df = 3 (P = 0.22); P = 29% Test for overall effect: Z = 0.04 (P = 0.97) C Sudy or Subgroup Events Total Events Total Events Total Weight M-H. Fixed, 95% Cl Cosnes 2002 19 49 239 589 55.4% 0.93 [0.51, 1.69] Naganuma 2001 8 21 156 304 30.8% 0.658 [0.24, 14.5] Selby 2002 5 12 50 239 6.9% 2.70 [0.82, 8.87] Total events 33 45 Heterogeneity: Ch <sup>2</sup> = 3.6, df = 3 (P = 0.23); P = 31% Test for overall effect: Z = 0.38 (P = 0.70) D Mult Fixed, 95% Cl Cosnes 2002 8 49 194 549 100.0% 0.92 [0.59, 1.43] Total events 33 45 Heterogeneity: Ch <sup>2</sup> = 4.36, df = 3 (P = 0.23); P = 31% Test for overall effect: Z = 0.38 (P = 0.70) D Mult Fixed, 95% Cl Cosnes 2002 8 49 194 549 100.0% 0.88 [0.54, 3.69] Picazo-Ferrera 2011 16 38 12 76 19.0% 3.88 [1.59, 9.46] Selby 2002 3 1 8 51 239 12.5% 2.08 [0.43, 1.78] Picazo-Ferrera 2011 16 38 12 76 19.0% 3.88 [1.59, 9.46] Selby 2002 4 2 808 20.5% 0.88 [0.41, 1.78] Halas 2004 9 202 424 808 20.5% 0.88 [0.41, 1.78] Heterogeneity: Ch <sup>2</sup> = 4.97 (P = 0.43); P = 72% Dotal (95% Cl) 345 4495 100.0% 1.38 [0.52, 3.04] Total (95% Cl) 345 4495 100.0% 1.38 [0.52, 3.04] Total events 42 497 Heterogeneity: Tau <sup>2</sup> = 0.65; Ch <sup>2</sup> = 18.05; df = 5 (P = 0.003); P = 72% Selby 2002 b 1 8 21 29 8.8% 1.48 [0.17, 12.64] Dotal (95% Cl) 345 4495 100.0% 1.38 [0.52, 3.04] Total events 42 497 Heterogeneity: Tau <sup>2</sup> = 0.65; Ch <sup>2</sup> = 18.05; df = 5 (P = 0.003); P = 72% Total (95% Cl) 345 4495 100.0% 1.38 [0.52, 3.04] Dotal events 42 497 (P = 0.03); P = 72% Total events 42 497 (P = 0.03); P = 72% Total events 42 497 (P = 0.03); P = 72%	Cosnes 2002	13	49	168	589	25.5%	0.90 [0.47, 1.75]	
Lee 2015 14 68 677 2544 37.7% 0.71 [0.39, 1.30] Naganuma 2001 5 21 93 304 12.3% 0.71 [0.25, 1.99] Selby 2002 5 8 69 239 2.3% 4.11 [0.96, 17.65] Total (95% Cl) 194 6459 100.0% 1.01 [0.73, 1.39] Total events 54 1753 Heterogeneity: Ch <sup>2</sup> = 7.02, df = 5 (P = 0.22); l <sup>2</sup> = 29% Test for overall effect: Z = 0.04 (P = 0.97) C Study or Subgroup Events Total Events Total Weight M-H. Fixed, 95% Cl 0.05 0.2 15 20 Favours [appendectomy] Favours [no appendectomy] C Study or Subgroup Events Total 250 239 7.0% 0.54 [0.06, 4.45] Selby 2002 5 12 50 239 6.5% 2.7 (D.82, 8.87] Total (95% Cl) 90 1371 100.0% 0.92 [0.59, 1.43] Total events 33 495 Heterogeneity: Ch <sup>2</sup> = 4.36, df = 3 (P = 0.23); l <sup>2</sup> = 31% Test for overall effect: 2 = 0.38 (P = 0.23); l <sup>2</sup> = 31% Total events 33 495 Heterogeneity: Ch <sup>2</sup> = 4.36, df = 3 (P = 0.23); l <sup>2</sup> = 31% Test for overall effect: 2 = 0.38 (P = 0.23); l <sup>2</sup> = 31% Test for overall effect: 2 = 0.38 (P = 0.70) D papendectomy no appendectomy Odds Ratio Odds Ratio Odds Ratio Odds Rati	Lee 2015	12	36	677	2544	17.0%	1.38 [0.69, 2.77]	
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	Lee 2015	14	68	677	2544	37.7%	0.71 [0.39, 1.30]	
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $	Naganuma 2001	5	21	93	304	12.3%	0.71 [0.25, 1.99]	
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $	Selby 2002	5	12	69	239	5.2%	1.76 [0.54, 5.73]	
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	Selby 2002	5	8	69	239	2.3%	4.11 [0.96, 17.65]	
Total (95% Cl)       194       6459       100.0%       1.01 [0.73, 1.39]         Total events       54       1753         Heterogeneity: Chi <sup>2</sup> = 7.02, df = 5 (P = 0.22); P = 29%       Test for overall effect: Z = 0.04 (P = 0.97)       C         C       appendectomy       no appendectomy       Odds Ratio         Study or Subgroup       Events       Total       Events       Total         Naganuma 2001       8       21       156       304       9.055 4.%       0.93 (0.51 1.69)         Selby 2002       5       12       50       239       7.0%       0.54 [0.06, 4.49]         Selby 2002       5       12       50       239       6.9%       2.70 [0.82, 8.87]         Total (95% Cl)       90       1371       100.0%       0.92 [0.59, 1.43]       0.05       0.2       1       5       20         Total events       33       495       4.46       6.9%       2.1%       0.05       0.2       1       5       20         Total events       0.38 (P = 0.23); P = 31%       Total Events       <								
Total events 54 1753 Heterogeneity: Chi <sup>2</sup> = 7.02, df = 5 (P = 0.22); l <sup>2</sup> = 29% Test for overall effect: Z = 0.04 (P = 0.97) C appendectomy no appendectomy Odds Ratio Study or Subgroup Events Total Events Total Weight M-H. Fixed, 95% Cl Naganuma 2001 8 21 156 304 30.8% 0.58 [0.24, 1.45] Selby 2002 5 12 50 239 6.9% 2.70 [0.82, 8.87] Total (95% Cl) 90 1371 100.0% 0.92 [0.59, 1.43] Total events 33 495 Heterogeneity: Chi <sup>2</sup> = 4.36, df = 3 (P = 0.23); l <sup>2</sup> = 31% Test for overall effect: Z = 0.38 (P = 0.70) D Study or Subgroup Events Total Events Total Weight M-H. Random, 95% Cl Cosnes 2002 8 49 194 559 20.1% 0.40 [0.18, 0.66] Haltas 2004 9 202 42 808 20.5% 0.45 [0.01, 1.76] Heterogeneity: Chi <sup>2</sup> = 4.36, df = 3 (P = 0.23); l <sup>2</sup> = 31% Total (95% Cl) 90 1371 100.0% 0.92 [0.59, 1.43] Total events 33 495 Heterogeneity: Chi <sup>2</sup> = 4.36, df = 3 (P = 0.23); l <sup>2</sup> = 31% Total Study or Subgroup Events Total Events Total Weight M-H. Random, 95% Cl Cosnes 2002 8 49 194 559 20.1% 0.40 [0.18, 0.66] Haltas 2004 9 202 42 808 20.5% 0.485 [0.41, 1.78] Heterogeneity: Tau <sup>2</sup> = 0.65; Chi <sup>2</sup> = 18.05, df = 5 (P = 0.03); l <sup>2</sup> = 72% Total (95% Cl) 345 4495 100.0% 1.38 [0.62, 3.04] Total events 42 497 Heterogeneity: Tau <sup>2</sup> = 0.65; Chi <sup>2</sup> = 18.05, df = 5 (P = 0.03); l <sup>2</sup> = 72% Total (95% Cl) 345 4495 100.0% 1.38 [0.62, 3.04] Total events 42 497 Heterogeneity: Tau <sup>2</sup> = 0.65; Chi <sup>2</sup> = 18.05, df = 5 (P = 0.03); l <sup>2</sup> = 72% Total events 42 497 Heterogeneity: Tau <sup>2</sup> = 0.79 (P = 0.43)	Total (95% CI)		194		6459	100.0%	1.01 [0.73, 1.39]	
Heterogeneity: Chi <sup>2</sup> = 7.02, df = 5 (P = 0.22); l <sup>2</sup> = 29%         Test for overall effect: Z = 0.04 (P = 0.97)         Odds Ratio	Total events	54		1753				
Test for overall effect: $Z = 0.04$ (P = 0.97) C appendectomy no appendectomy Odds Ratio Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% Cl Cosnes 2002 19 49 239 589 55.4% 0.93 [0.51, 1.69] Naganuma 2001 8 21 156 304 30.8% 0.58 [0.24, 1.45] Selby 2002 5 12 50 239 6.9% 2.70 [0.82, 8.87] Total (95% Cl) 90 1371 100.0% 0.92 [0.59, 1.43] Total events 33 495 Heterogeneity: Chi <sup>2</sup> = 4.36, df = 3 (P = 0.23);   <sup>2</sup> = 31% Test for overall effect: $Z = 0.38$ (P = 0.70) D Study or Subgroup Events Total Events Total Weight M-H. Random, 95% Cl Cosnes 2002 8 49 194 589 20.1% 0.40 [0.18, 0.86] Hallas 2004 9 202 42 808 20.5% 0.85 [0.41, 1.78] Lee 2015 a 6 36 207 2544 19.0% 2.26 [0.93, 5.49] Picazo-Errera 2011 16 38 12 76 19.0% 3.88 [1.59, 9.46] Selby 2002 a 2 12 21 239 12.5% 2.08 [0.43, 10.11] Selby 2002 b 1 8 21 239 8.8% 1.48 [0.17, 12.64] Total (95% Cl) 345 4495 100.0% 1.38 [0.62, 3.04] Total events 42 497 Heterogeneity: Tau <sup>2</sup> = 0.65, Chi <sup>2</sup> = 18.05, df = 5 (P = 0.003);   <sup>2</sup> = 72% Total (95% Cl) 345 4495 100.0% 1.38 [0.62, 3.04] Total events 42 497 Heterogeneity: Tau <sup>2</sup> = 0.76, Chi <sup>2</sup> = 18.05, df = 5 (P = 0.003);   <sup>2</sup> = 72% Total (95% Cl) 345 4495 100.0% 1.38 [0.62, 3.04]	Heterogeneity: Chi <sup>2</sup> =	7.02, df = 5 (	(P = 0.22	2); l² = 29%				0.05 0.2 1 5 20
C         appendectomy         no appendectomy         Odds Ratio           Study or Subgroup         Events         Total         Events         Total         Weight         M-H, Fixed, 95% CI         M-H, Fixed, 95% CI           Cosnes 2002         19         49         239         589         55.4%         0.93 [0.51, 1.69]         M-H, Fixed, 95% CI           Naganuma 2001         8         21         156         304         30.8%         0.58 [0.24, 1.45]           Selby 2002         5         12         50         239         7.0%         0.54 [0.06, 4.49]           Selby 2002         5         12         50         239         6.9%         2.70 [0.82, 8.87]           Total (95% CI)         90         1371         100.0%         0.92 [0.59, 1.43]           Total vevents         33         495           Heterogeneity: Chi <sup>2</sup> = 4.36, df = 3 (P = 0.23); l <sup>2</sup> = 31%         Favours [no appendectomy]         Favours [no appendectomy]           D         appendectomy         no appendectomy         Noda Ratio         Odds Ratio           Study or Subgroup         Events         Total         Veight         M-H, Random, 95% CI         M-H, Random, 95% CI           Conses 2002         8         49         194 <td< td=""><td>Test for overall effect:</td><td>Z = 0.04 (P =</td><td>= 0.97)</td><td></td><td></td><td></td><td></td><td></td></td<>	Test for overall effect:	Z = 0.04 (P =	= 0.97)					
Study or Subgroup         Events         Total         Events         Total         Weight         M-H, Fixed, 95% Cl         M-H, Fixed, 95% Cl           Cosnes 2002         19         49         239         589         55.4%         0.93 (0.51, 1.69]           Naganuma 2001         8         21         156         304         30.8%         0.58 [0.24, 1.45]           Selby 2002         1         8         50         239         7.0%         0.54 [0.06, 4.49]           Selby 2002         5         12         50         239         6.9%         2.70 [0.82, 8.87]           Total (95% Cl)         90         1371         100.0%         0.92 [0.59, 1.43]           Total events         33         495           Heterogeneity: Chi² = 4.36, df = 3 (P = 0.23); I² = 31%         Total Weight         M-H. Random. 95% Cl           D         appendectomy         no appendectomy         Odds Ratio         Odds Ratio           Study or Subgroup         Events         Total         Yeight         M-H. Random. 95% Cl           Cosnes 2002         8         49         194         589         20.1%         0.40 [0.18, 0.86]           Hallas 2004         9         202         42         808         2.05%		-	,					Favours [appendectomy] Favours [no appendectomy]
Situdy of Subgroup       Events       Total       Events       Total       Regult       Mediat       Me	С		, 				Odda Datia	Favours [appendectomy] Favours [no appendectomy]
Cosines 2022       19       49       239       50.4       1.45       0.35 [0.31, 1.05]         Naganuma 2001       8       21       156       304       30.8%       0.58 [0.24, 1.45]         Selby 2002       1       8       50       239       6.9%       2.70 [0.82, 8.87]         Total (95% CI)       90       1371       100.0%       0.92 [0.59, 1.43]         Total events       33       495         Heterogeneity: Chi² = 4.36, df = 3 (P = 0.23); l² = 31%       0.05       0.2       1       5       20         Total events       33       495       495       495       495       600 (0.18, 0.66)       600 (0.2       1       5       20         D       appendectomy       no appendectomy       Odds Ratio       Odds Ratio       Odds Ratio       Odds Ratio         Study or Subgroup       Events       Total       Events       Total       Weight       M-H. Random. 95% CI       M-H. Random. 95% CI         Cosnes 2002       8       49       194       589       20.1%       0.40 [0.18, 0.86]	C Study or Subgroup	appendec Events	tomy	no appende	ectomy Total	Weight	Odds Ratio	Favours [appendectomy] Favours [no appendectomy] Odds Ratio M.H. Fixed 95% Cl
Nagarum 201       0       21       130       304       304       30.3       0.36       [0.24, 1.43]         Selby 2002       1       8       50       239       7.0%       0.54       [0.06, 4.49]         Selby 2002       5       12       50       239       6.9%       2.70       [0.82, 8.87]         Total (95% Cl)       90       1371       100.0%       0.92       [0.59, 1.43]         Total events       33       495         Heterogeneity: Chi² = 4.36, df = 3 (P = 0.23); l² = 31%       Column 2       Column 2       Calue of the term 2       Column 2 <td>C Study or Subgroup</td> <td>appendec Events</td> <td>tomy <u>Total</u></td> <td>no appende Events</td> <td>ectomy Total</td> <td>Weight</td> <td>Odds Ratio <u>M-H, Fixed, 95% CI</u></td> <td>Pavours [appendectomy] Pavours [no appendectomy] Odds Ratio M-H, Fixed, 95% Cl</td>	C Study or Subgroup	appendec Events	tomy <u>Total</u>	no appende Events	ectomy Total	Weight	Odds Ratio <u>M-H, Fixed, 95% CI</u>	Pavours [appendectomy] Pavours [no appendectomy] Odds Ratio M-H, Fixed, 95% Cl
Selby 2002       5       12       50       233       1.0%       0.34 [0.00, 4.49]         Selby 2002       5       12       50       239       6.9%       2.70 [0.82, 8.87]         Total (95% Cl)       90       1371       100.0%       0.92 [0.59, 1.43]         Total events       33       495         Heterogeneity: Chi² = 4.36, df = 3 (P = 0.23); I² = 31%       0.05       0.2       1       5       20         Test for overall effect: Z = 0.38 (P = 0.70)       no appendectomy       Odds Ratio       Odds Ratio       Odds Ratio         Study or Subgroup       Events       Total       Events       Total       Weight       M-H, Random, 95% Cl       M-H, Random, 95% Cl         Cosnes 2002       8       49       194       589       20.1%       0.40 [0.18, 0.86]       M-H, Random, 95% Cl         Hallas 2004       9       202       42       808       20.5%       0.85 [0.41, 1.78]         Lee 2015 a       6       36       207       2544       19.0%       3.88 [1.59, 9.46]	C <u>Study or Subgroup</u> Cosnes 2002 Nacapuma 2001	appendec Events 19	tomy Total 49	no appende Events 239	ectomy Total 589	Weight 55.4%	Odds Ratio <u>M-H, Fixed, 95% CI</u> 0.93 [0.51, 1.69] 0.58 [0.24, 1.45]	Pavours [appendectomy] Pavours [no appendectomy] Odds Ratio M-H, Fixed, 95% Cl
Total (95% Cl)       90       1371       100.0%       0.92 [0.59, 1.43]         Total events       33       495         Heterogeneity: Chi <sup>2</sup> = 4.36, df = 3 (P = 0.23); l <sup>2</sup> = 31% $0.05$ $0.2$ $1$ $5$ $20$ D       appendectomy       no appendectomy       Odds Ratio       Odds Ratio       Odds Ratio         Study or Subgroup       Events       Total       Events       Total       Weight       M-H. Random. 95% Cl       M-H. Random. 95% Cl         Cosnes 2002       8       49       194       589       20.1%       0.40 [0.18, 0.86] $$	C Study or Subgroup Cosnes 2002 Naganuma 2001 Selby 2002	appendec Events 19 8	tomy <u>Total</u> 49 21	no appende Events 239 156 50	ectomy <u>Total</u> 589 304 239	Weight 55.4% 30.8% 7.0%	Odds Ratio <u>M-H, Fixed, 95% CI</u> 0.93 [0.51, 1.69] 0.58 [0.24, 1.45] 0.54 [0.06, 4.49]	Pavours [appendectomy] Pavours [no appendectomy] Odds Ratio M-H, Fixed, 95% Cl
Total (95% Cl)       90       1371       100.0%       0.92 [0.59, 1.43]         Total events       33       495         Heterogeneity: Chi <sup>2</sup> = 4.36, df = 3 (P = 0.23); l <sup>2</sup> = 31% $0.05$ $0.2$ $1$ $5$ $20$ Test for overall effect: Z = 0.38 (P = 0.70)       appendectomy       no appendectomy       Odds Ratio       Odds Ratio         Study or Subgroup       Events       Total       Events       Total       Events       Total       Weight       M-H. Random. 95% Cl       M-H. Random. 95% Cl         Cosnes 2002       8       49       194       589       20.1%       0.40 [0.18, 0.86] $$	C Study or Subgroup Cosnes 2002 Naganuma 2001 Selby 2002 Selby 2002	appendec Events 19 8 1	tomy <u>Total</u> 49 21 8 12	no appende Events 239 156 50 50	<b>Ectomy</b> Total 589 304 239 239	Weight 55.4% 30.8% 7.0% 6.9%	Odds Ratio <u>M-H, Fixed, 95% CI</u> 0.93 [0.51, 1.69] 0.58 [0.24, 1.45] 0.54 [0.06, 4.49] 2 70 [0.82, 8.87]	Pavours [appendectomy] Pavours [no appendectomy] Odds Ratio M-H, Fixed, 95% Cl
Total events       33       495         Heterogeneity: $Chi^2 = 4.36$ , $df = 3$ (P = 0.23); $ ^2 = 31\%$ 0.05       0.2       1       5       20         Test for overall effect: $Z = 0.38$ (P = 0.70)       no appendectomy       no appendectomy       Odds Ratio       Odds Ratio         D       appendectomy       no appendectomy       Total       Weight       M-H, Random, 95% Cl       M-H, Random, 95% Cl         Cosnes 2002       8       49       194       589       20.1%       0.40 [0.18, 0.86]       M-H, Random, 95% Cl         Hallas 2004       9       202       42       808       20.5%       0.85 [0.41, 1.78]         Lee 2015 a       6       36       207       2544       19.0%       2.26 [0.93, 5.49]       M-H, Random, 95% Cl         Picazo-Ferrera 2011       16       38       12       76       19.0%       3.88 [1.59, 9.46]       4.48 [0.17, 12.64]         Total (95% Cl)       345       4495       100.0%       1.38 [0.62, 3.04]       4.48 [0.17, 12.64]         Total events       42       497       4495       100.0%       1.38 [0.62, 3.04]       0.1       1       10       100         Total events       42       497       4495       100.0%       1.38 [0.62, 3.04] </td <td>C Study or Subgroup Cosnes 2002 Naganuma 2001 Selby 2002 Selby 2002</td> <td>appendec Events 19 8 1 5</td> <td>tomy <u>Total</u> 49 21 8 12</td> <td>no appende Events 239 156 50 50</td> <td><b>Ectomy</b> Total 589 304 239 239</td> <td>Weight 55.4% 30.8% 7.0% 6.9%</td> <td>Odds Ratio <u>M-H, Fixed, 95% CI</u> 0.93 [0.51, 1.69] 0.58 [0.24, 1.45] 0.54 [0.06, 4.49] 2.70 [0.82, 8.87]</td> <td>Pavours [appendectomy] Pavours [no appendectomy] Odds Ratio M-H, Fixed, 95% Cl</td>	C Study or Subgroup Cosnes 2002 Naganuma 2001 Selby 2002 Selby 2002	appendec Events 19 8 1 5	tomy <u>Total</u> 49 21 8 12	no appende Events 239 156 50 50	<b>Ectomy</b> Total 589 304 239 239	Weight 55.4% 30.8% 7.0% 6.9%	Odds Ratio <u>M-H, Fixed, 95% CI</u> 0.93 [0.51, 1.69] 0.58 [0.24, 1.45] 0.54 [0.06, 4.49] 2.70 [0.82, 8.87]	Pavours [appendectomy] Pavours [no appendectomy] Odds Ratio M-H, Fixed, 95% Cl
Heterogeneity: $Chi^2 = 4.36$ , $df = 3$ (P = 0.23); $ ^2 = 31\%$ Test for overall effect: $Z = 0.38$ (P = 0.70)         D       appendectomy       no appendectomy       Odds Ratio         Odds Ratio         Study or Subgroup       Events       Total       Weight       M-H, Random, 95% CI         Cosnes 2002       8       49       194<589       20.1%       0.40 [0.18, 0.86]         Halas 2004       9       202       42       88       19.0%       2.26 [0.93, 5.49]         Picazo-Ferrera 2011       16       38       12       76       19.0%       3.88 [1.59, 9.46]         Selby 2002 a       2       12       21       239       8.8%       1.48 [0.17, 12.64]         Total (95% CI)       345       4495       100.0%       1.38 [0.62, 3.04]         Total (95% CI)       345       4497       0.01       0.01	C Study or Subgroup Cosnes 2002 Naganuma 2001 Selby 2002 Selby 2002 Total (95% CI)	appendec Events 19 8 1 5	tomy <u>Total</u> 49 21 8 12 <b>90</b>	no appende Events 239 156 50 50	ectomy Total 589 304 239 239 1371	Weight 55.4% 30.8% 7.0% 6.9% 100.0%	Odds Ratio M-H, Fixed, 95% CI 0.93 [0.51, 1.69] 0.58 [0.24, 1.45] 0.54 [0.06, 4.49] 2.70 [0.82, 8.87] 0.92 [0.59, 1.43]	Pavours [appendectomy] Pavours [no appendectomy] Odds Ratio M-H, Fixed, 95% Cl
0.003       0.02       20         Favours [appendectomy]       Favours [no appendectomy]         D       Favours [no appendectomy]       Favours [no appendectomy]         Odds Ratio         Odds Ratio         Odds Ratio         Odds Ratio         Odds Ratio         Cosnes 2002       8       49       194       589       20.1%       Odds Ratio         Cosnes 2002       8       49       194       589       20.1%       0.40 [0.18, 0.86]         Hallas 2004       9       202       42       808       20.5%       0.86 [0.41, 1.78]         Picazo-Ferrera 2011       16       38       12       21       239       8.8%       1.48 [0.17, 12.64]         Total (95% CI)       345       4495       100.0%       1.38 [0.62, 3.04]       0.01       0.01       0.01 <th< td=""><td>C Study or Subgroup Cosnes 2002 Naganuma 2001 Selby 2002 Selby 2002 Total (95% CI) Total events</td><td>appendec Events 19 8 1 5 33</td><td>tomy <u>Total</u> 49 21 8 12 <b>90</b></td><td>no appende Events 239 156 50 50 495</td><td><b>Total</b> 589 304 239 239 1<b>371</b></td><td>Weight 55.4% 30.8% 7.0% 6.9% 100.0%</td><td>Odds Ratio M-H, Fixed, 95% CI 0.93 [0.51, 1.69] 0.58 [0.24, 1.45] 0.54 [0.06, 4.49] 2.70 [0.82, 8.87] 0.92 [0.59, 1.43]</td><td>Pavours [appendectomy] Pavours [no appendectomy] Odds Ratio M-H, Fixed, 95% Cl</td></th<>	C Study or Subgroup Cosnes 2002 Naganuma 2001 Selby 2002 Selby 2002 Total (95% CI) Total events	appendec Events 19 8 1 5 33	tomy <u>Total</u> 49 21 8 12 <b>90</b>	no appende Events 239 156 50 50 495	<b>Total</b> 589 304 239 239 1 <b>371</b>	Weight 55.4% 30.8% 7.0% 6.9% 100.0%	Odds Ratio M-H, Fixed, 95% CI 0.93 [0.51, 1.69] 0.58 [0.24, 1.45] 0.54 [0.06, 4.49] 2.70 [0.82, 8.87] 0.92 [0.59, 1.43]	Pavours [appendectomy] Pavours [no appendectomy] Odds Ratio M-H, Fixed, 95% Cl
$ \begin{array}{c ccccccccccccccccccccccccccccccccccc$	C <u>Study or Subgroup</u> Cosnes 2002 Naganuma 2001 Selby 2002 Selby 2002 <b>Total (95% CI)</b> Total events Heterogeneity: Chi <sup>2</sup> = -	appendec <u>Events</u> 19 8 1 5 33 4.36, df = 3 (	tomy <u>Total</u> 49 21 8 12 90 (P = 0.23	no appende <u>Events</u> 239 156 50 50 495 8);   <sup>2</sup> = 31%	<b>Total</b> 589 304 239 239 1371	Weight 55.4% 30.8% 7.0% 6.9% 100.0%	Odds Ratio M-H, Fixed, 95% CI 0.93 [0.51, 1.69] 0.58 [0.24, 1.45] 0.54 [0.06, 4.49] 2.70 [0.82, 8.87] 0.92 [0.59, 1.43]	Odds Ratio M-H, Fixed, 95% Cl
Study or Subgroup         Events         Total         Events         Total         Weight         M-H, Random, 95% Cl         M-H, Random, 95% Cl           Cosnes 2002         8         49         194         589         20.1%         0.40 [0.18, 0.86]         M-H, Random, 95% Cl           Hallas 2004         9         202         42         808         20.5%         0.85 [0.41, 1.78]           Lee 2015 a         6         36         207         2544         19.0%         2.26 [0.93, 5.49]           Picazo-Ferrera 2011         16         38         12         76         19.0%         3.88 [1.59, 9.46]           Selby 2002 a         2         12         21         239         12.5%         2.08 [0.43, 10.11]           Selby 2002 b         1         8         21         239         8.8%         1.48 [0.17, 12.64]           Total (95% Cl)         345         4495         100.0%         1.38 [0.62, 3.04]	C Study or Subgroup Cosnes 2002 Naganuma 2001 Selby 2002 Selby 2002 Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = - Test for overall effect:	<b>appendec</b> <b>Events</b> 19 8 1 5 33 4.36, df = 3 ( Z = 0.38 (P	tomy <u>Total</u> 49 21 8 12 90 (P = 0.23 = 0.70)	no appende Events 239 156 50 50 495 3);   <sup>2</sup> = 31%	<b>Total</b> 589 304 239 239 1371	Weight 55.4% 30.8% 7.0% 6.9% 100.0%	Odds Ratio M-H, Fixed, 95% CI 0.93 [0.51, 1.69] 0.58 [0.24, 1.45] 0.54 [0.06, 4.49] 2.70 [0.82, 8.87] 0.92 [0.59, 1.43]	Odds Ratio M-H, Fixed, 95% Cl 0.05 0.2 1 5 20 Fayours [appendectomy]
Cosnes 2002       8       49       194       589       20.1%       0.40 [0.18, 0.86]         Hallas 2004       9       202       42       808       20.5%       0.85 [0.41, 1.78]         Lee 2015 a       6       36       207       2544       19.0%       2.26 [0.93, 5.49]         Picazo-Ferrera 2011       16       38       12       76       19.0%       3.88 [1.59, 9.46]         Selby 2002 a       2       12       21       239       12.5%       2.08 [0.43, 10.11]         Selby 2002 b       1       8       21       239       8.8%       1.48 [0.17, 12.64]         Total (95% CI)       345       4495       100.0%       1.38 [0.62, 3.04]         Total events       42       497         Heterogeneity: Tau <sup>2</sup> = 0.65; Chi <sup>2</sup> = 18.05, df = 5 (P = 0.003); l <sup>2</sup> = 72%       0.01       0.1       1       10       100	C Study or Subgroup Cosnes 2002 Naganuma 2001 Selby 2002 Selby 2002 Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = - Test for overall effect: D	appendec <u>Events</u> 19 8 1 5 33 4.36, df = 3 ( Z = 0.38 (P	tomy <u>Total</u> 49 21 8 12 <b>90</b> (P = 0.23 = 0.70) comy	no appende <u>Events</u> 239 156 50 50 495 3); l <sup>2</sup> = 31%	ectomy <u>Total</u> 589 304 239 239 1371 ctomy	Weight 55.4% 30.8% 7.0% 6.9% 100.0%	Odds Ratio M-H, Fixed, 95% CI 0.93 [0.51, 1.69] 0.58 [0.24, 1.45] 0.54 [0.06, 4.49] 2.70 [0.82, 8.87] 0.92 [0.59, 1.43] Odds Ratio	Odds Ratio M-H, Fixed, 95% Cl 0.05 0.2 1 5 20 Favours [appendectomy] Favours [no appendectomy] Odds Ratio
Hallas 2004       9       202       42       808       20.5%       0.85 [0.41, 1.78]         Lee 2015 a       6       36       207       2544       19.0%       2.26 [0.93, 5.49]         Picazo-Ferrera 2011       16       38       12       76       19.0%       3.88 [1.59, 9.46]         Selby 2002 a       2       12       21       239       12.5%       2.08 [0.43, 10.11]         Selby 2002 b       1       8       21       239       8.8%       1.48 [0.17, 12.64]         Total (95% CI)       345       4495       100.0%       1.38 [0.62, 3.04]         Total events       42       497         Heterogeneity: Tau <sup>2</sup> = 0.65; Chi <sup>2</sup> = 18.05, df = 5 (P = 0.003); l <sup>2</sup> = 72%       0.01       0.1       1       10       100	C Study or Subgroup Cosnes 2002 Naganuma 2001 Selby 2002 Selby 2002 Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = - Test for overall effect: D Study or Subgroup	appendec <u>Events</u> 19 8 1 5 33 4.36, df = 3 ( Z = 0.38 (P appendect Events	tomy <u>Total</u> 49 21 8 12 90 (P = 0.23 = 0.70) comy Total	no appende <u>Events</u> 239 156 50 50 495 3); l <sup>2</sup> = 31% no appended Events	ectomy <u>Total</u> 589 304 239 239 1371 stomy Total	Weight 55.4% 30.8% 7.0% 6.9% 100.0% Weight	Odds Ratio <u>M-H, Fixed, 95% CI</u> 0.93 [0.51, 1.69] 0.58 [0.24, 1.45] 0.54 [0.06, 4.49] 2.70 [0.82, 8.87] 0.92 [0.59, 1.43] Odds Ratio M-H, Random, 95% Cl	Odds Ratio M-H, Fixed, 95% Cl 0.05 0.2 1 5 20 Favours [appendectomy] Odds Ratio M-H, Random, 95% Cl
Lee 2015 a       6       36       207       2544       19.0%       2.26 [0.93, 5.49]         Picazo-Ferrera 2011       16       38       12       76       19.0%       3.88 [1.59, 9.46]         Selby 2002 a       2       12       21       239       12.5%       2.08 [0.43, 10.11]         Selby 2002 b       1       8       21       239       8.8%       1.48 [0.17, 12.64]         Total (95% CI)       345       4495       100.0%       1.38 [0.62, 3.04]         Total events       42       497         Heterogeneity: Tau <sup>2</sup> = 0.65; Chi <sup>2</sup> = 18.05, df = 5 (P = 0.003); l <sup>2</sup> = 72%       0.01       0.1       1       10       100	C Study or Subgroup Cosnes 2002 Naganuma 2001 Selby 2002 Selby 2002 Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = - Test for overall effect: D Study or Subgroup Cosnes 2002	appendec <u>Events</u> 19 8 1 5 33 4.36, df = 3 ( Z = 0.38 (P appendect <u>Events</u> 8	tomy <u>Total</u> 49 21 8 12 90 (P = 0.23 = 0.70) comy <u>Total</u> 49	no appende <u>Events</u> 239 156 50 50 495 3); l <sup>2</sup> = 31% no appended <u>Events</u> 194	ectomy <u>Total</u> 589 304 239 239 1371 stomy <u>Total</u> 589	Weight 55.4% 30.8% 7.0% 6.9% 100.0% Weight 20.1%	Odds Ratio <u>M-H, Fixed, 95% CI</u> 0.93 [0.51, 1.69] 0.58 [0.24, 1.45] 0.54 [0.06, 4.49] 2.70 [0.82, 8.87] 0.92 [0.59, 1.43] Odds Ratio <u>M-H, Random, 95% CI</u> 0.40 [0.18, 0.86]	Odds Ratio M-H, Fixed, 95% Cl 0.05 0.2 1 5 20 Favours [appendectomy] Odds Ratio M-H, Random, 95% Cl
Picazo-Ferrera 2011       16       38       12       76       19.0%       3.88       [1.59, 9.46]         Selby 2002 a       2       12       21       239       12.5%       2.08       [0.43, 10.11]         Selby 2002 b       1       8       21       239       8.8%       1.48       [0.17, 12.64]         Total (95% CI)       345       4495       100.0%       1.38       [0.62, 3.04]         Total events       42       497         Heterogeneity: Tau <sup>2</sup> = 0.65; Chi <sup>2</sup> = 18.05, df = 5 (P = 0.003); l <sup>2</sup> = 72%       0.01       0.1       1       10       100	C Study or Subgroup Cosnes 2002 Naganuma 2001 Selby 2002 Selby 2002 Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = - Test for overall effect: D Study or Subgroup Cosnes 2002 Hallas 2004	appendect Events 19 8 1 5 33 4.36, df = 3 ( Z = 0.38 (P Events 8 9	tomy <u>Total</u> 49 21 8 12 90 (P = 0.23 = 0.70) comy <u>Total</u> 49 202	no appende <u>Events</u> 239 156 50 50 495 3); l <sup>2</sup> = 31% no appended <u>Events</u> 194 42	ectomy <u>Total</u> 589 304 239 239 1371 stomy <u>Total</u> 589 808	Weight 55.4% 30.8% 7.0% 6.9% 100.0% Weight 20.1% 20.5%	Odds Ratio <u>M-H, Fixed, 95% CI</u> 0.93 [0.51, 1.69] 0.58 [0.24, 1.45] 0.54 [0.06, 4.49] 2.70 [0.82, 8.87] 0.92 [0.59, 1.43] Odds Ratio <u>M-H, Random, 95% CI</u> 0.40 [0.18, 0.86] 0.85 [0.41, 1.78]	Pavours [appendectomy] Odds Ratio M-H, Fixed, 95% Cl 
Selby 2002 a       2       12       21       239       12.5%       2.08 [0.43, 10.11]         Selby 2002 b       1       8       21       239       8.8%       1.48 [0.17, 12.64]         Total (95% Cl)       345       4495       100.0%       1.38 [0.62, 3.04]         Total events       42       497         Heterogeneity: Tau <sup>2</sup> = 0.65; Chi <sup>2</sup> = 18.05, df = 5 (P = 0.003); l <sup>2</sup> = 72%       0.01       0.1       1       10       100         Test for overall effect: Z = 0.79 (P = 0.43)       1.38 <t< td=""><td>C Study or Subgroup Cosnes 2002 Naganuma 2001 Selby 2002 Selby 2002 Total (95% Cl) Total events Heterogeneity: Chi<sup>2</sup> = - Test for overall effect: D Study or Subgroup Cosnes 2002 Hallas 2004 Lee 2015 a</td><td>appendect Events 19 8 1 5 33 4.36, df = 3 ( Z = 0.38 (P appendect Events 8 9 6</td><td>tomy <u>Total</u> 49 21 8 12 <b>90</b> (P = 0.23 = 0.70) tomy <u>Total</u> 49 202 36</td><td>no appende 239 156 50 50 495 3); I<sup>2</sup> = 31% no appender Events 194 42 207</td><td>ectomy <u>Total</u> 589 304 239 239 1371 <b>total</b> 589 808 2544</td><td>Weight 55.4% 30.8% 7.0% 6.9% 100.0% Weight 20.1% 20.5% 19.0%</td><td>Odds Ratio <u>M-H, Fixed, 95% CI</u> 0.93 [0.51, 1.69] 0.58 [0.24, 1.45] 0.54 [0.06, 4.49] 2.70 [0.82, 8.87] 0.92 [0.59, 1.43] Odds Ratio <u>M-H, Random, 95% CI</u> 0.40 [0.18, 0.86] 0.85 [0.41, 1.78] 2.26 [0.93, 5.49]</td><td>Pavours [appendectomy] Odds Ratio M-H, Fixed, 95% Cl 0.05 0.2 1 5 20 Favours [appendectomy] Favours [no appendectomy] Odds Ratio M-H, Random, 95% Cl</td></t<>	C Study or Subgroup Cosnes 2002 Naganuma 2001 Selby 2002 Selby 2002 Total (95% Cl) Total events Heterogeneity: Chi <sup>2</sup> = - Test for overall effect: D Study or Subgroup Cosnes 2002 Hallas 2004 Lee 2015 a	appendect Events 19 8 1 5 33 4.36, df = 3 ( Z = 0.38 (P appendect Events 8 9 6	tomy <u>Total</u> 49 21 8 12 <b>90</b> (P = 0.23 = 0.70) tomy <u>Total</u> 49 202 36	no appende 239 156 50 50 495 3); I <sup>2</sup> = 31% no appender Events 194 42 207	ectomy <u>Total</u> 589 304 239 239 1371 <b>total</b> 589 808 2544	Weight 55.4% 30.8% 7.0% 6.9% 100.0% Weight 20.1% 20.5% 19.0%	Odds Ratio <u>M-H, Fixed, 95% CI</u> 0.93 [0.51, 1.69] 0.58 [0.24, 1.45] 0.54 [0.06, 4.49] 2.70 [0.82, 8.87] 0.92 [0.59, 1.43] Odds Ratio <u>M-H, Random, 95% CI</u> 0.40 [0.18, 0.86] 0.85 [0.41, 1.78] 2.26 [0.93, 5.49]	Pavours [appendectomy] Odds Ratio M-H, Fixed, 95% Cl 0.05 0.2 1 5 20 Favours [appendectomy] Favours [no appendectomy] Odds Ratio M-H, Random, 95% Cl
Selby 2002 b       1       8       21       239       8.8%       1.48 [0.17, 12.64]         Total (95% Cl)       345       4495       100.0%       1.38 [0.62, 3.04]         Total events       42       497         Heterogeneity: Tau <sup>2</sup> = 0.65; Chi <sup>2</sup> = 18.05, df = 5 (P = 0.003); l <sup>2</sup> = 72%       0.01       0.1       1       10       100         Test for overall effect: Z = 0.79 (P = 0.43)       1.38       0.01       0.1       1       10       100	C Study or Subgroup Cosnes 2002 Naganuma 2001 Selby 2002 Selby 2002 Total (95% Cl) Total events Heterogeneity: Chi <sup>2</sup> = - Test for overall effect: D Study or Subgroup Cosnes 2002 Hallas 2004 Lee 2015 a Picazo-Ferrera 2011	appendect Events 19 8 1 5 33 4.36, df = 3 ( Z = 0.38 (P appendect Events 8 9 6 16	tomy Total 49 21 8 12 90 (P = 0.23 = 0.70) tomy Total 49 202 36 38	no appende 239 156 50 50 495 3); I <sup>2</sup> = 31% no appendee Events 194 42 207 12	ectomy Total 589 304 239 239 1371 1371 589 808 2544 76	Weight 55.4% 30.8% 7.0% 6.9% 100.0% 20.0% 20.1% 20.1% 19.0%	Odds Ratio <u>M-H, Fixed, 95% CI</u> 0.93 [0.51, 1.69] 0.58 [0.24, 1.45] 0.54 [0.06, 4.49] 2.70 [0.82, 8.87] 0.92 [0.59, 1.43] Odds Ratio <u>M-H, Random, 95% CI</u> 0.40 [0.18, 0.86] 0.85 [0.41, 1.78] 2.26 [0.93, 5.49] 3.88 [1.59, 9.46]	Pavours [appendectomy] Odds Ratio M-H, Fixed, 95% Cl 0.05 0.2 1 5 20 Favours [appendectomy] Odds Ratio M-H, Random, 95% Cl M-H, Random, 95% Cl
Total (95% CI)       345       4495       100.0%       1.38 [0.62, 3.04]         Total events       42       497         Heterogeneity: Tau <sup>2</sup> = 0.65; Chi <sup>2</sup> = 18.05, df = 5 (P = 0.003); l <sup>2</sup> = 72%       0.01       0.1       1       10       100         Test for overall effect: Z = 0.79 (P = 0.43)       0.43       0.01       0.1       1       10       100	C Study or Subgroup Cosnes 2002 Naganuma 2001 Selby 2002 Selby 2002 Total (95% Cl) Total events Heterogeneity: Chi <sup>2</sup> = - Test for overall effect: D Study or Subgroup Cosnes 2002 Hallas 2004 Lee 2015 a Picazo-Ferrera 2011 Selby 2002 a	appendect Events 19 8 1 5 33 4.36, df = 3 ( Z = 0.38 (P = 3) appendect Events 8 9 6 16 2	tomy Total 49 21 8 12 90 (P = 0.23 = 0.70) comy Total 49 202 36 38 12	no appende Events 239 156 50 495 3); I <sup>2</sup> = 31% no appendee Events 194 42 207 12 21	ectomy <u>Total</u> 589 304 239 239 1371 ctomy <u>Total</u> 589 808 2544 76 239	Weight 55.4% 30.8% 7.0% 6.9% 100.0% 20.0% 19.0% 19.0% 19.0% 19.0%	Odds Ratio <u>M-H, Fixed, 95% CI</u> 0.93 [0.51, 1.69] 0.58 [0.24, 1.45] 0.54 [0.06, 4.49] 2.70 [0.82, 8.87] 0.92 [0.59, 1.43] Odds Ratio <u>M-H. Random, 95% CI</u> 0.40 [0.18, 0.86] 0.85 [0.41, 1.78] 2.26 [0.93, 5.49] 3.88 [1.59, 9.46] 2.08 [0.43, 10.11]	Pavours [appendectomy] Odds Ratio M-H. Fixed, 95% Cl 
Total events       42       497       1.36 [0.02, 0.04]         Heterogeneity:       Tau = 0.65; Chi <sup>2</sup> = 18.05, df = 5 (P = 0.003); l <sup>2</sup> = 72%       0.01       0.1       1       10       100         Test for overall effect: $Z = 0.79$ (P = 0.43)       0.01       0.1       1       10       100	C Study or Subgroup Cosnes 2002 Naganuma 2001 Selby 2002 Selby 2002 Total (95% Cl) Total events Heterogeneity: Chi <sup>2</sup> = - Test for overall effect: D Study or Subgroup Cosnes 2002 Hallas 2004 Lee 2015 a Picazo-Ferrera 2011 Selby 2002 a Selby 2002 b	appendect Events 19 8 1 5 33 4.36, df = 3 ( Z = 0.38 (P appendect Events 8 9 6 16 2 1	tomy Total 49 21 8 12 90 (P = 0.23 = 0.70) comy Total 49 202 36 38 12 8	no appende 239 156 50 50 495 3); I <sup>2</sup> = 31% no appende Events 194 42 207 12 21 21	ectomy Total 589 304 239 239 1371 589 808 2544 76 239 239	Weight 55.4% 30.8% 7.0% 6.9% 100.0% 20.0% 20.1% 20.1% 20.5% 19.0% 19.0% 12.5% 8.8%	Odds Ratio <u>M-H, Fixed, 95% C1</u> 0.93 [0.51, 1.69] 0.58 [0.24, 1.45] 0.54 [0.06, 4.49] 2.70 [0.82, 8.87] 0.92 [0.59, 1.43] Odds Ratio <u>M-H, Random, 95% C1</u> 0.40 [0.18, 0.86] 0.85 [0.41, 1.78] 2.26 [0.93, 5.49] 3.88 [1.59, 9.46] 2.08 [0.43, 10.11] 1.48 [0.17, 12.64]	Pavours [appendectomy] Odds Ratio M-H, Fixed, 95% Cl 
Hotar events $42$ $497$ Heterogeneity: Tau <sup>2</sup> = 0.65; Chi <sup>2</sup> = 18.05, df = 5 (P = 0.003); l <sup>2</sup> = 72%       0.01       0.1       1       10       100         Test for overall effect: Z = 0.79 (P = 0.43)       0.01       0.1       1       10       100	C Study or Subgroup Cosnes 2002 Naganuma 2001 Selby 2002 Selby 2002 Total (95% Cl) Total events Heterogeneity: Chi <sup>2</sup> = - Test for overall effect: D Study or Subgroup Cosnes 2002 Hallas 2004 Lee 2015 a Picazo-Ferrera 2011 Selby 2002 a Selby 2002 b Total (95% Cl)	appendect Events 19 8 1 5 33 4.36, df = 3 ( Z = 0.38 (P appendect Events 8 9 6 16 2 1	tomy Total 49 21 8 12 90 (P = 0.23 = 0.70) tomy Total 49 202 36 38 12 8 345	no appende 239 156 50 50 495 3); I <sup>2</sup> = 31% no appender Events 194 42 207 12 21 21	ectomy Total 589 304 239 239 1371 589 808 2544 76 239 239	Weight 55.4% 30.8% 7.0% 6.9% 100.0% 20.1% 20.1% 20.5% 19.0% 19.0% 19.0% 12.5% 8.8%	Odds Ratio <u>M-H, Fixed, 95% CI</u> 0.93 [0.51, 1.69] 0.58 [0.24, 1.45] 0.54 [0.06, 4.49] 2.70 [0.82, 8.87] 0.92 [0.59, 1.43] Odds Ratio <u>M-H, Random, 95% CI</u> 0.40 [0.18, 0.86] 0.85 [0.41, 1.78] 2.26 [0.93, 5.49] 3.88 [1.59, 9.46] 2.08 [0.43, 10.11] 1.48 [0.17, 12.64]	Pavours [appendectomy] Odds Ratio M-H, Fixed, 95% Cl 0.05 0.2 1 5 20 Favours [appendectomy] Favours [no appendectomy] Odds Ratio M-H, Random, 95% Cl
Test for overall effect: $Z = 0.79$ (P = 0.43) 0.01 0.1 1 10 100	C Study or Subgroup Cosnes 2002 Naganuma 2001 Selby 2002 Selby 2002 Total (95% Cl) Total events Heterogeneity: Chi <sup>2</sup> = - Test for overall effect: D Study or Subgroup Cosnes 2002 Hallas 2004 Lee 2015 a Picazo-Ferrera 2011 Selby 2002 a Selby 2002 b Total (95% Cl) Total overta	appendect Events 19 8 1 5 33 4.36, df = 3 ( Z = 0.38 (P 2 = 0.38 (P Events 8 9 6 16 2 1	tomy Total 49 21 8 12 90 (P = 0.22 = 0.70) comy Total 49 202 36 38 12 8 345	no appende 239 156 50 50 495 3); I <sup>2</sup> = 31% no appendee Events 194 42 207 12 21 21 21	ectomy Total 589 304 239 239 1371 589 808 2544 76 239 239 4495	Weight 55.4% 30.8% 7.0% 6.9% 100.0% 20.1% 20.1% 20.5% 19.0% 19.0% 12.5% 8.8% 100.0%	Odds Ratio M-H, Fixed, 95% CI 0.93 [0.51, 1.69] 0.58 [0.24, 1.45] 0.54 [0.06, 4.49] 2.70 [0.82, 8.87] 0.92 [0.59, 1.43] Odds Ratio M-H, Random, 95% CI 0.40 [0.18, 0.86] 0.85 [0.41, 1.78] 2.26 [0.93, 5.49] 3.88 [1.59, 9.46] 2.08 [0.43, 10.11] 1.48 [0.17, 12.64] 1.38 [0.62, 3.04]	Pavours [appendectomy] Odds Ratio M-H, Fixed, 95% Cl 0.05 0.2 1 5 20 Favours [appendectomy] Odds Ratio M-H, Random, 95% Cl M-H, Random, 95% Cl
	C Study or Subgroup Cosnes 2002 Naganuma 2001 Selby 2002 Selby 2002 Total (95% Cl) Total events Heterogeneity: Chi <sup>2</sup> = - Test for overall effect: D Study or Subgroup Cosnes 2002 Hallas 2004 Lee 2015 a Picazo-Ferrera 2011 Selby 2002 a Selby 2002 b Total (95% Cl) Total events Heterogeneity: Tau <sup>2</sup> = 0	appendect Events 19 8 1 5 33 4.36, df = 3 ( Z = 0.38 (P appendect Events 8 9 6 16 2 1 42 0.65, Chi <sup>2</sup> = -	tomy Total 49 21 8 12 90 (P = 0.23 = 0.70) tomy Total 49 202 36 38 12 8 345 18 05 cff	no appende Events 239 156 50 495 3); $I^2 = 31\%$ no appendee Events 194 42 207 12 21 21 21 21 21 21 21	Total           589           304           239           1371           ctomy           Total           589           808           2544           76           239           4495           301/16 = 72	Weight 55.4% 30.8% 7.0% 6.9% 100.0% Weight 20.1% 19.0% 19.0% 19.0% 12.5% 8.8% 100.0%	Odds Ratio M-H, Fixed, 95% CI 0.93 [0.51, 1.69] 0.58 [0.24, 1.45] 0.54 [0.06, 4.49] 2.70 [0.82, 8.87] 0.92 [0.59, 1.43] Odds Ratio M-H. Random, 95% CI 0.40 [0.18, 0.86] 0.85 [0.41, 1.78] 2.26 [0.93, 5.49] 3.88 [1.59, 9.46] 2.08 [0.43, 10.11] 1.48 [0.17, 12.64] 1.38 [0.62, 3.04]	Pavours [appendectomy] Odds Ratio M-H, Fixed, 95% Cl 

Fig. 3. Results for comparison II. A. Proctitis. B. Left-sided colitis. C. Pancolitis. D. Colectomy.

		Table	IV. Outcomes o	f this meta-a	nalysis				
	Ct. roline	No. of pa	rticipants	Heter	ogeneity	10000	Efi	fect size	2
Outcomes	Studies	Case	Control	b	d	Niodel	OR	95% CI	d
Comparison I: UC patients vs healthy control									
Previous appendectomy	11	4,673	6,216	82%	< 0.0001	Ж	0.44	(0.30, 0.64)	< 0.0001
Comparison II: UC patients under appendecto	omy vs no ap	<i>pendectomy</i>							
Proctitis-overall	4	194	6,459	44%	0.11	ш	1.03	(0.74, 1.42)	0.87
Subgroup-before UC diagnosis	4	114	3,676	48%	0.21	ш	1.10	(0.70, 1.73)	0.68
Subgroup-after UC diagnosis	2	44	2,783	24%	0.25	ш	0.87	(0.47, 1.62)	0.66
Left-sided colitis	4	194	6,459	29%	0.22	ш	1.01	(0.73, 1.39)	0.97
Subgroup-before UC diagnosis	4	114	3,676	%0	0.56	ш	1.07	(0.72, 1.61)	0.74
Subgroup-after UC diagnosis	2	44	2,783	43%	0.19	ш	1.70	(0.92, 3.14)	0.09
Pancolitis	m	06	1,371	31%	0.23	ш	0.92	(0.59, 1.43)	0.70
Subgroup-before UC diagnosis	m	78	1,132	%0	0.66	ш	0.78	(0.48, 1.27)	0.33
Subgroup-after UC diagnosis	1	00	239	ı	ı	ı	0.54	(0.06, 4.49)	0.57
Colectomy	Ŋ	345	4,495	72%	0.003	Ж	1.38	(0.62, 3.04)	0.43
Subgroup-before UC diagnosis	m	97	3,372	80%	0.007	Ж	1.15	(0.31, 4.30)	0.83
Subgroup-after UC diagnosis	2	210	1,047	%0	0.63	ш	0.80	(0.45, 1.80)	0.75
Subgroup- before/after UC diagnosis	<del>, -</del>	38	76	I	I	I	0.20	(0.10, 0.40)	0.003
Comparison III: UC patients AOI positive vs AC	Ol negative								
Proctitis	4	123	313	29%	0.24	ш	1.15	(0.67, 1.98)	0.61
Left-sided colitis	2	102	271	87%	0.005	ĸ	1.14	(0.24, 5.42)	0.87
Surgical therapy	m	116	296	%0	0.96	ш	0.36	(0.10, 1.23)	0.10
UC: Ulcerative colitis; AOI: Appendiceal orifice inflamm:	lation; F: Fixed e	iffect model; R: Ra	ndom effect model;	OR: Odds ratio;	CI: Confidence inte	rval.			

The results showed that appendectomy before or after UC diagnosis did not statistically affect the severity of UC (p > 0.05); however, there was a report for both before/after UC diagnosis (33) showing a significant difference (p = 0.003).

#### **Results of comparison III: combined AOI did not** affect the severity and surgical treatment rate of UC patients

The results of comparison III were shown in figure 4. The influence of combined AOI in the severity of UC was studied in four articles (15-17,29) including 436 subjects (AOI positive: 123; AOI negative: 313). There was significant heterogeneity among studies for left-sided colitis and the random effects model was used for merging of the effect sizes, while no heterogeneity was found among the studies for proctitis and the fixed effect model was used. Pooled results showed that there were no statistical significance in severity of UC between patients combined with AOI and those not combined with AOI (proctitis: OR = 1.15, 95% CI [0.67, 1.98], p = 0.61; left-sided colitis: OR = 1.14, 95% CI [0.24, 5.42], p = 0.87). Meanwhile, there was also no significant difference in surgical treatment rate for UC patients (OR = 1.36, 95% CI [0.10, 1.23], p = 0.10). These results indicate that combined AOI did not affect the severity and surgical treatment rate.

#### Sensitivity analysis and publication bias

No reverse occurred after removing any of the studies (data not shown), which indicates that the present results were robust.

The funnel plot of comparison I showed that there was no significant publication bias (Fig. 2B). Publication bias for other comparisons was not performed because of the limited amount of literature.

А	AOI pos	sitive	AOI nec	ative		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% CI
Byeon 2005	38	48	30	46	26.5%	2.03 [0.80, 5.10]	+
Naves 2011	11	14	21	25	13.4%	0.70 [0.13, 3.69]	
W. Brian 1999	1	7	0	17	1.0%	8.08 [0.29, 224.49]	
Yamagishi 2002	8	54	43	225	59.0%	0.74 [0.32, 1.67]	
Total (95% CI)		123		313	100.0%	1.15 [0.67, 1.98]	•
Total events	58		94				
Heterogeneity: Chi <sup>2</sup> =	4.24, df = 3	3 (P = 0	.24); l² = 2	9%			
Test for overall effect:	Z = 0.51 (F	⊃ = 0.61	)				Eavours [AO] positive] Eavours [AO] pegative
R							
D	AOI pos	itive	AOI nega	ative		Odds Ratio	Odds Ratio
Study or Subaroup	Events	Total	Events	Total	Weiaht	M-H. Random, 95% C	M-H. Random, 95% Cl
Byeon 2005	10	48	16	46	47.5%	0.49 [0.20, 1.24]	
Yamagishi 2002	25	54	59	225	52.5%	2.43 [1.32, 4.47]	-=-
Total (95% CI)		102		271	100.0%	1.14 [0.24, 5.42]	
Total events	35		75				
Heterogeneity: Tau <sup>2</sup> =	1.11; Chi <sup>2</sup> =	= 7.96, c	lf = 1 (P =	0.005);	l² = 87%		
Test for overall effect:	Z = 0.16 (P	= 0.87)					Favours [ AOI positive] Favours [ AOI negative
С							
-	AOI pos	sitive	AOI neg	gative		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% Cl
Byeon 2005	0	48	1	46	13.6%	0.31 [0.01, 7.87]	
Naves 2011	0	14	1	25	9.5%	0.56 [0.02, 14.76]	
Yamagishi 2002	2	54	23	225	76.9%	0.34 [0.08, 1.48]	
Total (95% CI)		116		296	100.0%	0.36 [0.10, 1.23]	
Total events	2		25				
Heterogeneity: Chi <sup>2</sup> =	0.09, df = 2	2 (P = 0	.96); l² = 0	)%			
Test for overall effect:	Z = 1.63 (I	P = 0.10	))				0.001 0.1 1 10 1000
	- (		,				Favours [AOI positive] Favours [ AOI negative

Fig. 4. Results for comparison III. A. Proctitis. B. Left-sided colitis. C. Surgery therapy.

#### DISCUSSION

This meta-analysis including 19 case-control studies comprehensively compared the influences of appendectomy and AOI in risk and severity of UC. The strengths of this study were the comprehensive analysis, the high quality of the studies included (NOS 6-8) and its robust results (sensitivity analysis). The results showed that appendectomy reduced the risk of UC but, as well as AOI, it did not affect its courses.

Firstly, comparison I confirmed that appendectomy was a protective factor of UC (OR = 0.44 [95% CI: 0.30-0.64], p < 0.0001). This is not consistent with the previous meta-analysis which indicated that the risk of CD, another IBD, significantly increased in the early years after appendectomy (RR = 1.99) (35). This disparity might be caused by the different mechanisms of the disease and the heterogeneity among studies. Heterogeneity in comparison I mainly comes from the study of Ko 2015a, which was performed among Middle Eastern migrants who were in a specific environment (19). Thus, we can still speculate that appendectomy or AOI may relate to the development of UC.

Scholars proposed that appendectomy before diagnosis only delayed the onset of UC but it did not reduce the risk (30). We therefore conducted comparison II to test whether appendectomy affected UC courses. The results indicated that in UC patients appendectomy did not affect the severity of UC and the need for surgery. This is consistent with the previous study, which implies that appendectomy protects against the development of UC but does not affect its course (36).

The influence of time between appendectomy and IBD diagnosis should be taken into account (35). In this study, subgroup analysis by appendectomy time was conducted and the results showed that appendectomy before or after UC diagnosis did not statistically affect the severity of UC. However, we did not stratify the time after UC diagnosis as the study conducted by Kaplan et al. did (35) due to the limited data, which is one of the disadvantages of the present study.

A long-term outcome study of Naves et al. (29) indicated that patients with AOI tend to present a mild course, and the chance to develop proximal progression of disease extent or colectomy was reduced. We finally analyzed the courses of UC in patients with AOI positive and AOI negative in comparison III. The meta-analysis of four studies, including the study by Naves et al. (2011) (29), indicated that there was no significant association between AOI and the extent of UC patient to develop proctitis, left-sided colitis and pancolitis, and the need of colectomy.

However, interpretation of the results in comparison III should be cautious due to the following reasons. First, the small sample size in comparisons II and III may influence the study conclusions; thus, it needs support from largescale studies. Second, there were heterogeneities among studies for colectomy in comparison II and for left-sided colitis in comparison III. The possible sources, the difference in age when appendectomy was performed, the difference in subtypes of UC and the difference in nursing levels among diverse areas could affect the clinical courses and treatment of UC. Though the random effects model was used for merging effect sizes, there might also be influences in the observations.

In conclusion, this meta-analysis confirmed that appendectomy can reduce the risk of UC. But AOI or appendectomy had no influence on the severity of the UC disease and the effect of surgical treatment.

#### REFERENCES

- Klement G, Huang P, Mayer B, et al. Differences in therapeutic indexes of combination metronomic chemotherapy and an anti-VEGFR-2 antibody in multidrug-resistant human breast cancer xenografts. Clin Cancer Res 2002;8:221-32.
- Sugiyama Y, Saji S, Miya K, et al. Therapeutic effect of multimodal therapy, such as cryosurgery, locoregional immunotherapy and systemic chemotherapy against far advanced breast cancer. Gan To Kagaku Ryoho 2001;28:1616-9.
- Scroussi B, Bouaud J, Antoine EC. Users' evaluation of OncoDoc, a breast cancer therapeutic guideline delivered at the point of care. Proc AMIA Symp 1999:384-9.
- 4. Goldstone R, Itzkowitz S, Harpaz N, et al. Dysplasia is more common in the distal than proximal colon in ulcerative colitis surveillance. Inflamm Bowel Dis 2012;18:832-7. DOI: 10.1002/ibd.21809
- Castiglione F, Diaferia M, Morace F, et al. Risk factors for inflammatory bowel diseases according to the "hygiene hypothesis": A casecontrol, multi-centre, prospective study in Southern Italy. J Crohns Colitis 2012;6:324-9. DOI: 10.1016/j.crohns.2011.09.003
- Florin TH, Pandeya N, Radford-Smith GL. Epidemiology of appendicectomy in primary sclerosing cholangitis and ulcerative colitis: Its influence on the clinical behaviour of these diseases. Gut 2004;53:973-9. DOI: 10.1136/gut.2003.036483
- Gearry RB, Richardson AK, Frampton CM, et al. Population-based cases control study of inflammatory bowel disease risk factors. J Gastroenterol Hepatol 2010;25:325-33. DOI: 10.1111/j.1440-1746.2009.06140.x
- Inoue K, Tabei T, Suemasu K, et al. Therapeutic efficacy of pirarubicin cyclophosphamide and doxifluridine in advanced and metastatic breast cancer. Gan To Kagaku Ryoho 1999;26:637-42.
- Alexandre J, Faivre S, Sutherland W, et al. Effects of adjuvant chemotherapy on the natural history and likelihood of therapeutic efficacy in advanced breast cancer patients: A critical literature review. Cancer Treat Rev 1998;24:393-406. DOI: 10.1016/S0305-7372(98)90002-0
- Valero V, Hortobagyi GN. Primary chemotherapy: A better overall therapeutic option for patients with breast cancer. Ann Oncol 1998;9:1151-4. DOI: 10.1023/A:1008427218935
- 11. Namer M, Ramaioli A, Hery M, et al. Prognostic factors and therapeutic strategy of breast cancer. Rev Prat 1998;48:45-51.
- Samarel N, Fawcett J, Davis MM, et al. Effects of dialogue and therapeutic touch on preoperative and postoperative experiences of breast cancer surgery: An exploratory study. Oncol Nurs Forum 1998;25:1369-76.
- Elstner E, Williamson EA, Zang C, et al. Novel therapeutic approach: Ligands for PPARgamma and retinoid receptors induce apoptosis in bcl-2-positive human breast cancer cells. Breast Cancer Res Treat 2002;74:155-65. DOI: 10.1023/A:1016114026769
- Huber S, Ulsperger E, Gomar C, et al. Osseous metastases in breast cancer: Radiographic monitoring of therapeutic response. Anticancer Res 2002;22:1279-88.
- 15. Byeon JS, Yang SK, Myung SJ, et al. Clinical course of distal ulcerative colitis in relation to appendiceal orifice inflammation

status. Inflamm Bowel Dis 2005;11:366-71. DOI: 10.1097/01.MIB. 0000164018.06538.6e

- Perry WB, Opelka FG, Smith D, et al. Discontinuous appendiceal involvement in ulcerative colitis: Pathology and clinical correlation. J Gastrointest Surg 1999;3:141-4. DOI: 10.1016/S1091-255X (99)80023-7
- Yamagishi N, Iizuka B, Nakamura T, et al. Clinical and colonoscopic investigation of skipped periappendiceal lesions in ulcerative colitis. Scand J Gastroenterol 2002;37:177-82. DOI: 10.1080/ 003655202753416849
- Park SH, Loftus EV Jr, Yang SK. Appendiceal skip inflammation and ulcerative colitis. Dig Dis Sci 2014;59:2050-7. DOI: 10.1007/s10620-014-3129-z
- Ko Y, Kariyawasam V, Karnib M, et al. Inflammatory bowel disease environmental risk factors: A population-based case-control study of Middle Eastern migration to Australia. Clin Gastroenterol Hepatol 2015;13:1453-63e1. DOI: 10.1016/j.cgh.2015.02.045
- Selby WS, Griffin S, Abraham N, et al. Appendectomy protects against the development of ulcerative colitis but does not affect its course. Am J Gastroenterol 2002;97:2834-8. DOI: 10.1111/j.1572-0241.2002.07049.x
- Wells G, Shea B, O'connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in metaanalyses. 2000.
- Higgins J, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. BMJ 2003;327:557-60. DOI: 10.1136/bmj.327. 7414.557
- Cosnes J, Carbonnel F, Beaugerie L, et al. Effects of appendicectomy on the course of ulcerative colitis. Gut 2002;51:803-7. DOI: 10.1136/ gut.51.6.803
- Hallas J, Gaist D, Vach W, et al. Appendicectomy has no beneficial effect on admission rates in patients with ulcerative colitis. Gut 2004;53:351-4. DOI: 10.1136/gut.2003.016915
- Hlavaty T, Toth J, Koller T, et al. Smoking, breastfeeding, physical inactivity, contact with animals, and size of the family influence the risk of inflammatory bowel disease: A Slovak case-control study. United European Gastroenterol J 2013;1:109-19. DOI: 10.1177/2050640613478011

- Lee HS, Park SH, Yang SK, et al. Appendectomy and the clinical course of ulcerative colitis: A retrospective cohort study and a nested case-control study from Korea. J Gastroenterol Hepatol 2015;30:470-7. DOI: 10.1111/jgh.12707
- López-Serrano P, Pérez-Calle JL, Pérez-Fernández MT, et al. Environmental risk factors in inflammatory bowel diseases. Investigating the hygiene hypothesis: A Spanish case-control study. Scand J Gastroenterol 2010;45:1464-71. DOI: 10.3109/00365521.2010.510575
- Naganuma M, Iizuka B, Torii A, et al. Appendectomy protects against the development of ulcerative colitis and reduces its recurrence: Results of a multicenter case-controlled study in Japan. Am J Gastroenterol 2001;96:1123-6. DOI: 10.1111/j.1572-0241.2001.03757.x
- Naves J E, Lorenzo-Zuniga V, Marín L, et al. Long-term outcome of patients with distal ulcerative colitis and inflammation of the appendiceal orifice. J Gastrointestin Liver Dis 2011;20:355-8.
- Radford-Smith GL, Edwards JE, Purdie DM, et al. Protective role of appendicectomy on onset and severity of ulcerative colitis and Crohn's disease. Gut 2002;51:808-13. DOI: 10.1136/gut.51.6.808
- Selby WS, Griffin S, Abraham N, et al. Appendectomy protects against the development of ulcerative colitis but does not affect its course. Am J Gastroenterol 2002;97:2834-8. DOI: 10.1111/j.1572-0241.2002.07049.x
- Wang YF, Ou-Yang Q, Xia B, et al. Multicenter case-control study of the risk factors for ulcerative colitis in China. World J Gastroenterol 2013;19:1827-33. DOI: 10.3748/wjg.v19.i11.1827
- Picazo-Ferrera K, Bustamante-Quan Y, Santiago-Hernández J, et al. The role of appendectomy in the ulcerative colitis in Mexico. Rev Gastroenterol Mex 2011;76:316-21.
- Uzan A, Jolly D, Berger E, et al. Protective effect of appendectomy on the development of ulcerative colitis. A case-control study. Gastroenterol Clin Biol 2001;25:239-42.
- Kaplan GG, Jackson T, Sands BE, et al. The risk of developing Crohn's disease after an appendectomy: A meta-analysis. Am J Gastroenterol 2008;103:2925-31. DOI: 10.1111/j.1572-0241.2008.02118.x
- 36. Selby WS, Griffin S, Abraham N, et al. Appendectomy protects against the development of ulcerative colitis but does not affect its course. Am J Gastroenterol 2002;97:2834-8. DOI: 10.1111/j.1572-0241.2002.07049.x