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REVIEW ARTICLE

Effect of Delay to Operation on Outcomes in Patients with Acute Appendicitis: a Systematic Review and Meta-analysis

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Abstract

Background Many studies have investigated the association between time interval and incidence of complicated appendicitis and post-operative surgical site infection (SSI), but the results are controversial.

Methods A systematic search of the electronic databases identified studies that investigated the association of appendectomy delay with complicated appendicitis and SSI among patients with acute appendicitis. Qualitative and quantitative meta-analysis of the results was conducted.

Results Twenty-one studies were included in the final analysis. Meta-analysis showed no significant difference in complicated appendicitis incidence between patients in the 6–12 h, > 12 and < 6 h groups (OR 1.07, 95% CI 0.89–1.30, $p = 0.47$; OR 1.04, 95% CI 0.88–1.22, $p = 0.64$). Comparison of the 6–12 h category with the < 6 h category of in-hospital delay revealed significant associations between longer in-hospital delay and increased risk of post-operative SSI (OR 1.40, 95% CI 1.11–1.77, $p = 0.004$). Patients in the 24–48 h category had 1.99- and 1.84-fold ($p < 0.05$) higher odds of developing complicated appendicitis compared to patients in the < 24 h category for pre-hospital delay and total delay, respectively (OR 1.99, 95% CI 1.35–2.94, $p = 0.0006$; OR 1.84, 95% CI 1.05–3.21, $p = 0.03$). When pre-hospital and total delay time extended to more than 48 h, the odds of risk increased 4.62- and 7.57-fold, respectively (OR 4.62, 95% CI 2.99–7.13, $p < 0.00001$; OR 7.57, 95% CI 6.14–9.35, $p = < 0.00001$).

Conclusion Complicated appendicitis incidence was associated with overall elapsed time from symptom onset to admission or operation; short appendectomy in-hospital delay did not increase the risk of complicated appendicitis but was associated with a slightly increased risk of SSI. Prompt surgical intervention is warranted to avoid additional morbidity, enabling quicker recovery in this population.

Keywords Acute appendicitis · Appendectomy · Delay · Surgical site infection

Introduction

Acute appendicitis is one of the most common intra-abdominal conditions, with a 9.0% lifetime cumulative incidence rate, and appendectomy is the most frequently performed emergency operation by general surgeons worldwide.[1] Despite significant advancements in diagnosis and treatment, the incidence of complicated acute appendicitis, including gangrenous or perforated appendicitis, remains considerably high (28–29%),[2,3] and post-operative morbidity rates remain between 9 and 18%.[4]

Although an instant emergent appendectomy has been the standard treatment for patients with acute appendicitis at the time of diagnosis, many controversies in the management of acute appendicitis have existed during the last century. Specifically, the timing of surgery for appendicitis has been continuously debated for the past 120 years and still remains unsolved, as reported in studies published worldwide.

The time-honoured notion that the "goal should be to accelerate diagnosis and to operate before perforation occurs" was based on pathophysiology of appendicitis described in the early twentieth century. This description proposes a progressive inflammatory process due to luminal obstruction and infection, which leads to increasing tension in the wall with

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ischaemia, necrosis and perforation.[5,6] Many studies have found a positive association between time interval and the risk of perforation, a long delay to operation results in complicated appendicitis and, as a consequence, post-operative morbidity.[7–11]

However, the concept of an emergency appendectomy has been challenged from child groups and adult groups by many studies in recent years. To avoid disrupting operating room schedules and to reduce technical errors associated with sleep deprivation and fatigue, it was shown to be safe to delay operation on uncomplicated acute appendicitis cases that present after hours until the next morning.[12,13] Moreover, the discoveries that spontaneous resolution may be a common event in patients with low-grade appendicitis and that acute appendicitis can be managed with a semi-elective strategy after antibiotic therapy have been initiated, further confusing the issue.[14–18]

In view of these inconsistent findings, we set out to perform this systematic review and meta-analysis to determine the association between time interval and incidence of complicated appendicitis. While surgical site infection (SSI) has been the most common post-operative morbidity after appendectomy, we also care about the association between delayed surgery and SSI in patients with acute appendicitis.

Methods

We performed this review in accordance with guidelines from the Meta-analysis of Observational Studies in Epidemiology (MOOSE) group and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for reporting meta-analyses.[19,20] We started the review in April 2017 and completed it in April 2018. Study collection, quality assessment and data extraction were performed by the investigators Yao Zhang and Deng-min Hu, disagreements were resolved by consensus, and where disagreement could not be solved, a third reviewer Jian Li resolved the conflict.

Literature Search and Eligibility Criteria

A systematic electronic search of Embase, Medline, PubMed, PubMed Central and Cochrane databases was performed from their initiation until 1 April 2018. The following search strategy was followed for all databases: (appendicitis OR appendectomy OR appendicectomy) AND (early OR delay* OR tim* OR rupture* OR perforat*). No restrictions were applied regarding to language or publication date. All search results were combined in a reference manager database (MedRef, version 5.0, Medlive, Beijing, China), and duplicates were removed. The titles and abstracts were reviewed to select full papers, and full-text studies were further evaluated. Reference lists of included studies and the 'related links' option in PubMed were used to screen for additional relevant studies. We did not try to find unpublished data by contacting experts in the field of acute appendicitis.

Studies meeting the following criteria were included: (1) design was a randomized controlled trial (RCT), prospective observational or retrospective cohort or case-control study; (2) studies dealt with the association between time interval and pathological degree of acute appendicitis, whether the delay was the main study variable or one of several factors under study, no matter the type of delay (e.g., pre-hospital, in-hospital or total); (3) time interval could be divided into < 6, 6–12, > 12 h and < 24, 24–48, > 48 h for in-hospital delay and pre-hospital or total delay, respectively, because it was applied to most of the studies; and (4) where there was overlap in patient cohorts between two studies, the study that contained the more recent and larger cohort was included. Studies were excluded according to the following criteria: (1) traditional reviews, editorials and opinion letters or comments**;** (2) studies that did not provide extractable data; and (3) the cut-off of time interval was set to another standard different from that mentioned above.

Quality Assessment

Study methodological quality was assessed by applying the Newcastle Ottawa Scale (NOS) for observational studies.[21] The NOS criteria included the following three items: patient selection, comparability and assessment of exposure or outcome. A study can be awarded a maximum of one score for each numbered item within the selection and assessment categories. NOS scores of ≥ 7 were considered high-quality studies and of 5–6 were considered of moderate quality.[22]

Data Extraction and Outcome Measure

The following information was extracted from each study: first author, country, year of publication, study period, study design, single or multicentre, number of patients (finally diagnosed pathologically, excluding patients with negative appendectomy or other reasons rather than acute appendicitis), age range of patients, definition of delay and complicated appendicitis, method to determine the time points (which was used to evaluate the accuracy of time interval record) and outcomes. We separated the time between onset of symptoms and starting of appendectomy (total delay) into two main phases: delay by patients, which we defined as pre-hospital delay, and delay by providers, which we defined as in-hospital delay. The outcome measure was the incidence of complicated appendicitis and post-operation SSI in each group according to delay time. Extracted data were entered into a pre-generated standard Microsoft Excel (Microsoft Corporation, Redmond, Washington, USA) file.

Statistical Analysis

Meta-analysis was performed using the RevMan software (Review Manager, version 5.3; The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark), while association between delay of appendectomy and incidence of complicated appendicitis or post-operative SSI was evaluated using odds ratio (OR) and 95% confidence interval (CI) calculated by the Mantel-Haenszel model. Due to the clinical heterogeneity of the patient groups and the inclusion of observational studies, a random effects model was used for all statistical analyses. Furthermore, we plan to conduct subgroup analyses examining the following pre-specified variables: sample size, age groups, publishing year, study location, study design, single or multicentre, definition of complicated appendicitis, with pre-surgical perforation excluded, symptom onset record accuracy and NOS score. Between-study heterogeneity was assessed using the I^2 statistic; it was determined that the values of 25, 50 and 75% in the I^2 test corresponded to low, medium, and high levels of heterogeneity, respectively. To assess for publication bias, visual inspection of the funnel plots was performed; an asymmetric plot indicated potential publication bias.[23] p values were two tailed, and differences of < 0.05 were deemed to be significant.

Results

Study Selection

A total of 3297 potentially relevant results were identified with the search strategies. After the exclusion of 1266 duplicates, 2031 remained for title-abstract screening, and full-text articles were then retrieved from 59 references. Finally, 21 studies were included in the qualitative and quantitative analysis.[8–10,17,18,24–39] The PRISMA flow diagram of study selection details is listed in Fig. 1.

Study Characteristics

A detailed overview of baseline characteristics and demographics is shown in Table 1. Studies were published

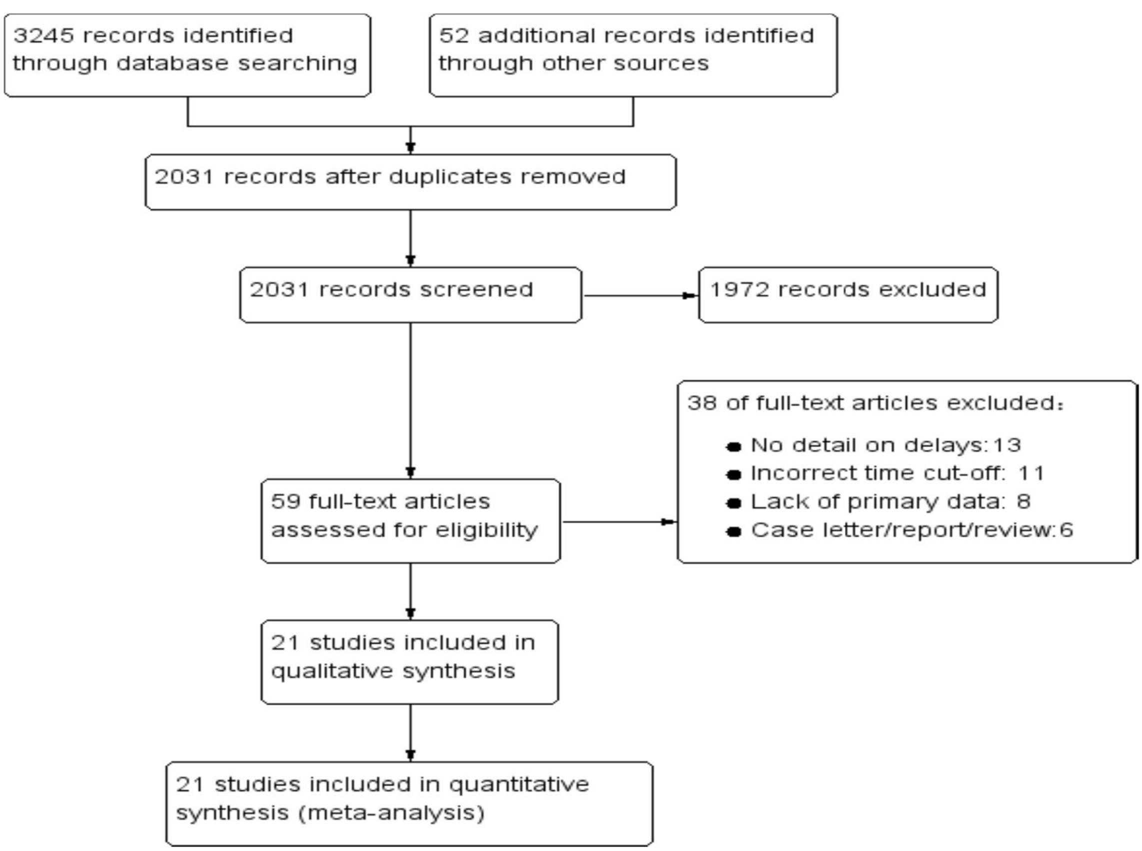


Fig. 1 Study flow diagram based on PRISMA recommendation

Table 1 Characteristics of the studies included in the meta-analysis

Author	Year	Country	Study period	Design	Cases*	Age (year)	Definition		
							Delay	Symptom onset record accuracy	Complicated appendicitis
Augustin et al.[24]	2011	USA	January 2000–June 2005	R	349	3–81	Total: symptom duration to perforation	Accurate	Perforated
Bickell et al.[8]	2006	USA	1996–1998	R	219	29.3	Pre-hospital: time not treated after symptom onset	Accurate	Rupture
Boomer et al.[25]	2014	USA	January 2010–December 2012	R	1388	≤ 18	In-hospital: admission to OR; total: symptom onset to OR	Less accurate	Gangrenous, perforated
Busch et al.[26]	2011	SUI	January 2003–January 2006	P	1675	> 16	In-hospital: admittance to operation	–	Perforated
Eko et al.[27]	2013	USA	January 2005–December 2007	R	354	3–86	In-hospital: ED registration to skin incision	–	Abscess, perforated, gangrenous
Eldar et al.[10]	1997	ISR	January 1980–December 1992	R	364	5–85	Pre-hospital: duration of complaints before admission; In-hospital: arrival at ED to surgery	Less accurate	Perforated, gangrenous
Fahim et al.[28]	2005	PAK	February 2002–April 2002	R	96	No restriction	Pre-hospital: duration of complaints before presentation; in-hospital: ED to surgery	Less accurate	Gangrenous, perforated
Gurien et al.[29]	2016	USA	January 2009–December 2012	R	484	10.5 ± 3.6	In-hospital: admission to OR	–	Perforated
Hansson et al.[30]	2008	SWE	February 1997–June 2000	P	253	2–89	Pre-hospital: duration before seeking medical advice; in-hospital: duration of pain before operation	Accurate	Gangrenous, perforated
Ingraham et al.[18]	2010	USA	January 2005–December 2008	R	32,782	≥ 16	In-hospital: surgical admission to induction of anaesthesia	–	Perforated, peritonitis, abscess
Jeon et al.[31]	2016	KOR	January 2008–December 2013	R	4148	33.8 ± 18.1	Total: symptom onset to surgery; in-hospital: hospital arrival to surgery	Accurate	Perforated
Kearney et al.[17]	2008	IRL	June 2005–June 2006	R	115	> 16	In-hospital: waiting times before operation	–	Perforated
Kim et al.[32]	2017	KOR	January 2010–December 2014	R	4065	32.8 ± 19.1	In-hospital: ED or first visited the initial hospital to general anaesthesia induction	–	Perforated
Lee et al.[33]	2018	KOR	January 2010–December 2013	R	1076	2–85	In-hospital: in-hospital delay; total: overall elapsed time	Less accurate	Gangrenous, perforated
Mandeville et al.[34]	2015	USA	May 2009–April 2010	P	230	4–17	Pre-hospital: symptom onset to diagnosis; in-hospital: diagnosis to surgery	Less accurate	Gangrenous, perforated
Maroju et al.[35]	2004	IND	April 1999–March 2000	P	111	13–56	Pre-hospital: onset of first symptom to presentation; in-hospital: physician related delay before surgery	Accurate	Gangrenous, perforated
Sammalkorpi et al.[36]	2015	FIN	January 2011–January 2012	P	389	16–94	In-hospital: initial physical examination at ED to surgery; total: onset of symptoms to surgery	Less accurate	In-hospital: perforated, abscess; total: gangrene, perforated, abscess
Saar et al.[37]	2016	EST	September 2013–December 2014	P	263	≥ 18	Total: onset of abdominal pain to surgery	Accurate	Gangrenous, perforated, abscess, diffuse peritonitis
Teixeira et al.[9]	2012	USA	June 2003–May 2011	R	4108	27.7 ± 14.5	In-hospital: admission to operation	–	Perforated
Yardeni et al.[38]	2004	USA	1998–2001	R	126	< 16	In-hospital: arrival in the ED to OR	–	Perforated
Stevenson et al.[39]	2017	USA	March 2009–April 2010	R	955	3–18	Pre-hospital: duration of abdominal pain before ED; in-hospital: ED evaluation to operation	Accurate	Ruptured, abscess

ED emergency department, *OR* operating room, *P* prospective, *R* retrospective, *SUI* Switzerland, *ISR* Israel, *PAK* Pakistan, *SWE* Sweden, *KOR* Korea, *IRL* Ireland, *IND* India, *FIN* Finland, *EST* Estonia

*No. patients included in meta-analysis

between 1997 and 2018 and consisted of 53,435 patients with acute appendicitis, with study sizes ranging from 96 to 32,782 patients. Regarding the type of delays, 15 studies were about the in-hospital delay, 8 studies referred to pre-hospital delay and 7 studies discussed total delay. Fifteen studies were retrospective, and six studies were prospective. Five studies were restricted to paediatric patients, 6 studies were strict to adult patients and 10 studies selected patients without age restriction. Seventeen studies were conducted in a single centre, while four studies in multicentre. In 10 studies, complicated appendicitis was referred to as gangrenous, perforated appendicitis and appendicular abscess, while 11 studies excluded the gangrenous appendicitis.

Risk of Bias

A major difficulty with most of the studies on the influence of delay on clinical outcome of patients with acute appendicitis was that the potential confounding effects of age, proficiency of surgeons and antibiotic selection bias were not taken into account. Only nine studies adjusted for other confounders, but their adjusted ORs were not suitable for our meta-analysis because of the different time cut-off. When studies discussed the association between delay of appendectomy and incidence of complicated appendicitis or post-operative SSI, only three studies excluded patients with a presumed pre-surgical perforation, which may lead to a selection bias. However, our aim was not to examine a new association between confounders and a perforation or SSI but rather to use a feature of an already established causal relation, so the question of study quality was not as relevant. Nevertheless, we examined study quality with the NOS, and the results are presented in Table 2. We also conducted subgroup analyses examining the confounding effect on outcomes of interest, and the results will be shown in the next part of this paper.

In-Hospital Delay and Complicated Appendicitis

Fifteen studies commented on the association between in-hospital delay and complicated appendicitis. Meta-analysis

Table 2 Risk of bias of studies included in the meta-analysis

Studies	Selection				Comparability		Outcome		
	Representativeness of exposed cohort	Selection of non-exposed cohort	Ascertainment of exposure	Demonstration that outcome was not known at start of study	Comparability of groups on the basis of analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur?	Adequacy of follow-up of cohorts	Total
Augustin et al.[24]	1	1	1	0	1	1	1	1	7
Bickell et al.[8]	1	1	1	0	2	1	1	1	8
Boomer et al.[25]	1	1	0	0	0	1	1	1	5
Busch et al.[26]	1	1	1	1	2	1	1	1	9
Eko et al.[27]	1	1	1	0	1	1	1	1	7
Eldar et al.[10]	1	1	0	0	2	1	1	1	7
Fahim et al.[28]	1	1	0	0	0	1	1	1	5
Gurien et al.[29]	1	1	1	1	2	1	1	1	9
Hansson et al.[30]	1	1	1	1	1	1	1	1	8
Ingraham et al.[18]	1	1	1	0	0	1	1	1	6
Jeon et al.[31]	1	1	1	0	2	1	1	1	8
Kearney et al.[17]	1	1	1	0	1	1	1	1	7
Kim et al.[32]	1	1	1	0	1	1	1	1	7
Lee et al.[33]	1	1	0	0	0	1	1	1	5
Mandeville et al.[34]	1	1	0	1	0	1	1	1	6
Maroju et al.[35]	1	1	1	1	0	1	1	1	7
Sammalkorpi et al.[36]	1	1	0	1	1	1	1	1	7
Saar et al.[37]	1	1	1	1	0	1	1	1	7
Teixeira et al.[9]	1	1	1	0	2	1	1	1	8
Yardeni et al.[38]	1	1	1	0	0	1	1	1	6
Stevenson et al.[39]	1	1	1	0	2	1	1	1	8

showed no significant difference in complicated appendicitis incidence between patients in the 6–12, > 12 and < 6 h group (OR 1.07, 95% CI 0.89–1.30, $p = 0.47$; OR 1.04, 95% CI 0.88–1.22, $p = 0.64$, respectively; Fig. 2). Most subgroup analyses further identified the same findings of the association (Table 3). When appendectomy was delayed to > 12 h, a slightly increased risk of complicated appendicitis was observed in patients from ≤ 2010 and Europe (OR 1.13, 95% CI 1.03–1.24, $p = 0.01$; OR 1.51, 95% CI 1.08–2.11, $p = 0.02$, respectively; Table 3).

In-Hospital Delay and SSI

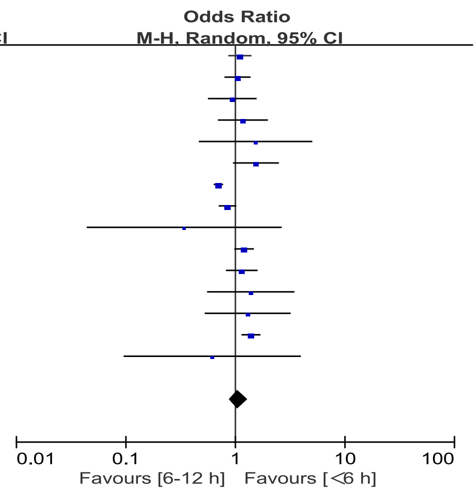
Four studies were included in the meta-analysis of in-hospital delay and risk of post-operative SSI. Comparison of the 6–12 h category with the < 6 h category of in-hospital delay revealed significant associations between longer in-hospital delay and increased risk of post-operative SSI (OR 1.40, 95% CI 1.11–1.77, $p = 0.004$, Fig. 3a). The heterogeneity between the included studies was not significant ($I^2 = 0\%$, $p = 0.77$). However, the significance disappeared when comparing the > 12 and < 6 h categories (OR 2.47, 95% CI 0.44–13.87, $p = 0.31$, Fig. 3b), and the heterogeneity increased significantly ($I^2 = 96\%$, $p = < 0.00001$). Subgroup analysis was not necessary because only four studies were involved.

Pre-hospital Delay and Complicated Appendicitis

Meta-analysis of eight studies showed that a 24–48-h delay to medical consultation increased complicated

Study or Subgroup	6-12 h Events	6-12 h Total	<6 h Events	<6 h Total	Weight	Odds Ratio M-H, Random, 95% CI
Boomer LA	197	546	265	781	9.8%	1.10 [0.87, 1.38]
Busch M	128	554	179	801	9.4%	1.04 [0.81, 1.35]
Eko FN	69	153	50	107	6.4%	0.94 [0.57, 1.54]
Eldar S	46	138	41	137	6.3%	1.17 [0.70, 1.95]
Fahim F	10	48	5	34	2.1%	1.53 [0.47, 4.95]
Gurien LA	42	147	54	262	6.8%	1.54 [0.97, 2.46]
Ingraham AM	730	5929	4120	24647	11.2%	0.70 [0.64, 0.76]
Jeon BG	232	1072	628	2555	10.5%	0.85 [0.71, 1.01]
Kearney D	3	25	2	7	0.8%	0.34 [0.04, 2.61]
Kim HK	233	1553	267	2084	10.3%	1.20 [0.99, 1.45]
Lee JM	115	395	97	367	8.7%	1.14 [0.83, 1.57]
Maroju NK	15	29	24	55	3.2%	1.38 [0.56, 3.41]
Sammalkorpi HE	12	100	10	105	3.3%	1.30 [0.53, 3.15]
Teixeira PG	305	1100	300	1384	10.3%	1.39 [1.15, 1.67]
Yardeni D	2	40	3	38	1.0%	0.61 [0.10, 3.89]
Total (95% CI)		**11829**		**33364**	**100.0%**	**1.07 [0.89, 1.30]**
Total events	2139		6045			

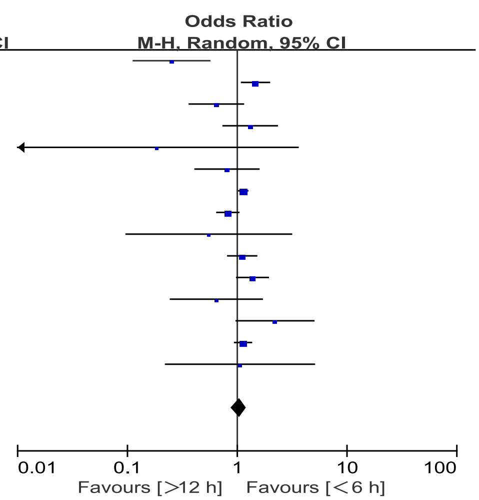
Heterogeneity: Tau² = 0.08; Chi² = 80.66, df = 14 (P < 0.00001); I² = 83%
Test for overall effect: Z = 0.72 (P = 0.47)



(a) 6–12 h VS <6 h

Study or Subgroup	>12 h Events	>12 h Total	<6 h Events	<6 h Total	Weight	Odds Ratio M-H, Random, 95% CI
Boomer LA	7	61	265	781	3.3%	0.25 [0.11, 0.56]
Busch M	95	320	179	801	10.8%	1.47 [1.10, 1.96]
Eko FN	34	94	50	107	5.5%	0.65 [0.37, 1.14]
Eldar S	32	89	41	137	5.5%	1.31 [0.75, 2.32]
Fahim F	0	14	5	34	0.3%	0.18 [0.01, 3.58]
Gurien LA	13	75	54	262	4.3%	0.81 [0.41, 1.58]
Ingraham AM	598	3201	4150	24647	15.8%	1.13 [1.03, 1.25]
Jeon BG	110	521	628	2555	12.5%	0.82 [0.65, 1.03]
Kearney D	15	83	2	7	0.8%	0.55 [0.10, 3.12]
Kim HK	60	428	267	2084	10.6%	1.11 [0.82, 1.50]
Lee JM	104	314	97	367	9.9%	1.38 [0.99, 1.92]
Maroju NK	9	27	24	55	2.4%	0.65 [0.25, 1.69]
Sammalkorpi HE	20	106	10	105	3.2%	2.21 [0.98, 4.98]
Teixeira PG	337	1414	300	1384	13.9%	1.13 [0.95, 1.35]
Yardeni D	4	48	3	38	1.0%	1.06 [0.22, 5.05]
Total (95% CI)		**6795**		**33364**	**100.0%**	**1.04 [0.88, 1.22]**
Total events	1438		6075			

Heterogeneity: Tau² = 0.04; Chi² = 35.93, df = 14 (P = 0.001); I² = 61%
Test for overall effect: Z = 0.47 (P = 0.64)



(b) >12 h VS <6 h

Fig. 2 Results and the forest plot from the main meta-analysis of studies on association between in-hospital delay and complicated appendicitis. M-H indicates Mantel-Haenszel method. **a** 6–12 vs < 6 h. **b** > 12 vs < 6 h

Table 3 Subgroup analyses of studies on association between in-hospital delay and complicated appendicitis

Subgroup	Studies	6–12 vs < 6 h		> 12 vs < 6 h	
		OR (95% CI)	Heterogeneity (P value, I^2)	OR (95% CI)	Heterogeneity (P value, I^2)
Overall	15	1.07 (0.89–1.30)	< 0.00001, 83%	1.04 (0.88–1.22)	0.001, 61%
Age					
Paediatric	3	1.17 (0.94–1.46)	0.35, 4%	0.55 (0.22–1.37)	0.06, 65%
Adult	5	0.90 (0.65–1.27)	0.01, 68%	1.24 (0.96–1.60)	0.12, 45%
No restriction	7	1.12 (0.93–1.34)	0.01, 64%	1.04 (0.86–1.26)	0.05, 52%
Publishing year					
≤2010	6	0.89 (0.63–1.27)	0.15, 38%	1.13 (1.03–1.24)	0.60, 0%
> 2010	9	1.12 (0.98–1.29)	0.02, 57%	1.01 (0.79–1.28)	0.0001, 75%
Study design					
Prospective	3	1.08 (0.85–1.37)	0.77,0%	1.38 (0.83–2.30)	0.15, 47%
Retrospective	12	1.06 (0.85–1.31)	< 0.00001, 86%	0.98 (0.83–1.17)	0.003, 61%
Study centre					
Single	13	1.13 (0.99–1.30)	0.06, 42%	0.95 (0.76–1.19)	0.003, 60%
Multi	2	0.84 (0.57–1.24)	0.004, 88%	1.24 (0.98–1.58)	0.10, 63%
Study location					
USA	6	1.06 (0.73–1.52)	< 0.00001, 91%	0.89 (0.68–1.16)	0.003, 72%
Europe	3	1.04 (0.82–1.34)	0.50, 0%	1.51 (1.08–2.11)	0.34, 8%
Asia	6	1.07 (0.89–1.29)	0.11, 45%	1.04 (0.81–1.34)	0.08, 49%
Perforation at admission excluded					
Yes	3	1.17 (0.78–1.77)	0.28, 22%	0.73 (0.48–1.11)	0.78, 0%
No	12	1.06 (0.86–1.30)	< 0.00001, 85%	1.08 (0.91–1.29)	0.009, 65%
Complicate appendicitis					
Perforated	8	1.13 (0.93–1.38)	0.006, 65%	1.11 (0.96–1.27)	0.07, 45%
Gangrenous, perforated	7	1.01 (0.77–1.33)	0.002, 77%	0.73 (0.41–1.29)	0.001, 76%
Cases					
≤ 500	8	1.20 (0.94–1.54)	0.74, 0%	0.94 (0.65–1.36)	0.21, 27%
> 500	7	1.03 (0.82–1.30)	< 0.00001, 91%	1.07 (0.89–1.29)	0.0003, 76%
NOS score					
≥ 7	10	1.13 (0.96–1.33)	0.02, 55%	1.05 (0.87–1.28)	0.03, 53%
< 7	5	0.96 (0.68–1.35)	0.0003, 81%	0.82 (0.50–1.35)	0.002, 76%

OR odds ratio, *CI* confidence interval

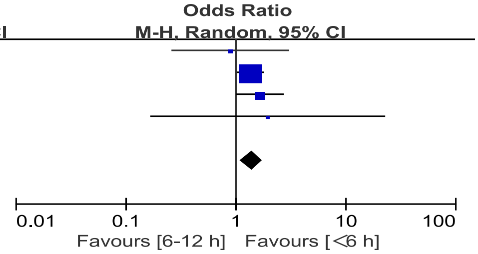
appendicitis incidence for patients with appendicitis; the pooled OR was 1.99 (95% CI 1.35–2.94, $p = 0.0006$; Fig. 4a), and the degree of heterogeneity was moderate ($I^2 = 71\%$, $p = 0.001$). As shown in Table 4, in the subgroup analysis of studies with a paediatric, prospective design, published after 2010, carried out in the USA and Europe, excluding gangrenous from complicated appendicitis, there was no significant correlation of 24–48 h delay with acute appendicitis incidence. When the pre-hospital delay was prolonged to more than 48 h, the pooled OR significantly increased to 4.62 (95% CI 2.99–7.13, $p < 0.00001$, Fig. 4b); although a high level of between-study heterogeneity existed ($I^2 = 76\%$, $p = 0.0002$), the adjustment for confounders did not change the positive association (Table 4).

Total Delay and Complicated Appendicitis

The risk of complicated appendicitis was increased (OR 1.84, 95% CI 1.05–3.21, $p = 0.03$; Fig. 5a) in patients who received appendectomy within 24–48 h after symptom onset and the between-study heterogeneity was significant ($I^2 = 83\%$, $p < 0.00001$), so a majority subgroup analysis no longer maintained such a result (Table 5). In regard to more than 48 h symptom duration before

Study or Subgroup	6-12 h Events	6-12 h Total	<6 h Events	<6 h Total	Weight	Odds Ratio M-H, Random, 95% CI
Gurien LA	4	147	8	262	3.6%	0.89 [0.26, 3.00]
Kim HK	111	1553	112	2084	72.6%	1.36 [1.03, 1.78]
Teixeira PG	39	1100	30	1384	22.9%	1.66 [1.02, 2.69]
Yardeni D	2	40	1	38	0.9%	1.95 [0.17, 22.40]
Total (95% CI)		**2840**		**3768**	**100.0%**	**1.40 [1.11, 1.77]**
Total events	156		151			

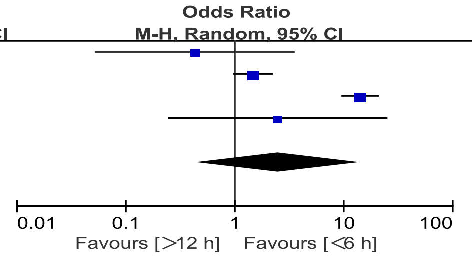
Heterogeneity: Tau² = 0.00; Chi² = 1.14, df = 3 (P = 0.77); I² = 0%
Test for overall effect: Z = 2.87 (P = 0.004)



(a) 6–12 h VS <6 h

Study or Subgroup	>12 h Events	>12 h Total	<6 h Events	<6 h Total	Weight	Odds Ratio M-H, Random, 95% CI
Gurien LA	1	75	8	262	20.9%	0.43 [0.05, 3.49]
Kim HK	33	428	112	2084	29.7%	1.47 [0.98, 2.20]
Teixeira PG	337	1413	30	1384	29.8%	14.14 [9.65, 20.71]
Yardeni D	3	48	1	38	19.6%	2.47 [0.25, 24.72]
Total (95% CI)		**1964**		**3768**	**100.0%**	**2.47 [0.44, 13.87]**
Total events	374		151			

Heterogeneity: Tau² = 2.57; Chi² = 73.13, df = 3 (P < 0.00001); I² = 96%
Test for overall effect: Z = 1.03 (P = 0.31)



(b) >12 h VS <6 h

Fig. 3 Results and the forest plot from the main meta-analysis of studies on association between in-hospital delay and SSI. M-H indicates Mantel-Haenszel method. **a** 6–12 vs < 6 h. **b** > 12 vs < 6 h

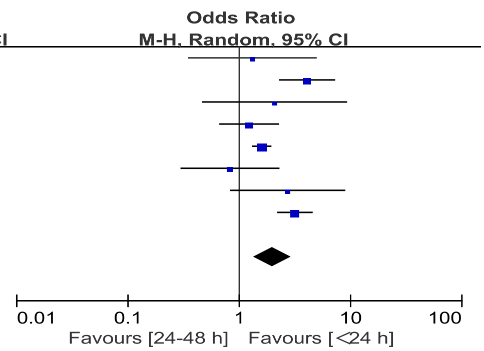
appendectomy, meta-analysis of all selected studies (OR 7.57, 95% CI 6.14–9.35, $p = < 0.00001$; $I^2 = 62\%$, $p = 0.02$; Fig. 5b) and subgroup analysis demonstrated a strong association between total delay and complicated appendicitis (Table 5).

Publication Bias

Publication bias is summarized by means of funnel plots only for outcomes of association between in-hospital delay and complicated appendicitis which included 15 studies (Fig. 6).

Study or Subgroup	24-48 h Events	24-48 h Total	<24 h Events	<24 h Total	Weight	Odds Ratio M-H, Random, 95% CI
Bickell NA	6	69	4	59	6.4%	1.31 [0.35, 4.88]
Eldar S	45	83	37	164	15.5%	4.06 [2.31, 7.16]
Fahim F	3	12	9	65	5.3%	2.07 [0.47, 9.15]
Hansson LE	38	65	70	131	14.9%	1.23 [0.67, 2.24]
Jeon BG	231	960	376	2265	21.9%	1.59 [1.32, 1.92]
Mandeville K	12	91	7	45	9.1%	0.82 [0.30, 2.26]
Maroju NK	7	19	9	51	7.4%	2.72 [0.84, 8.84]
Stevenson MD	93	278	73	532	19.4%	3.16 [2.23, 4.49]
Total (95% CI)		**1577**		**3312**	**100.0%**	**1.99 [1.35, 2.94]**
Total events	435		585			

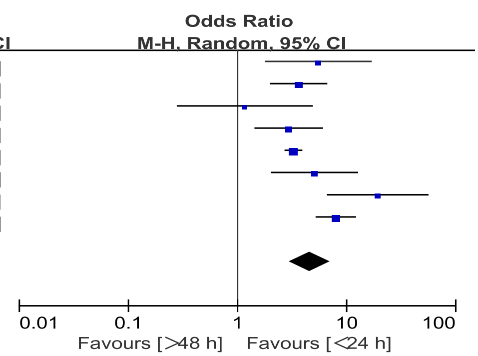
Heterogeneity: Tau² = 0.17; Chi² = 23.85, df = 7 (P = 0.001); I² = 71%
Test for overall effect: Z = 3.45 (P = 0.0006)



(a) 24–48 h VS < **24** h

Study or Subgroup	>48 h Events	>48 h Total	<24 h Events	<24 h Total	Weight	Odds Ratio M-H, Random, 95% CI
Bickell NA	26	91	4	59	8.7%	5.50 [1.81, 16.73]
Eldar S	37	72	37	164	14.8%	3.63 [2.01, 6.54]
Fahim F	3	19	9	65	6.4%	1.17 [0.28, 4.83]
Hansson LE	44	57	70	131	13.2%	2.95 [1.45, 5.98]
Jeon BG	363	923	376	2265	19.7%	3.26 [2.74, 3.87]
Mandeville K	45	93	7	45	10.8%	5.09 [2.06, 12.55]
Maroju NK	33	41	9	51	9.2%	19.25 [6.70, 55.33]
Stevenson MD	81	145	73	532	17.2%	7.96 [5.28, 12.00]
Total (95% CI)		**1441**		**3312**	**100.0%**	**4.62 [2.99, 7.13]**
Total events	632		585			

Heterogeneity: Tau² = 0.24; Chi² = 28.61, df = 7 (P = 0.0002); I² = 76%
Test for overall effect: Z = 6.89 (P < 0.00001)



(b) >48 h VS < **24** h

Fig. 4 Results and the forest plot from the main meta-analysis of studies on association between pre-hospital delay and complicated appendicitis. M-H indicates Mantel-Haenszel method. **a** 24–48 vs < 24 h. **b** > 48 vs < 24 h

Table 4 Subgroup analyses of studies on association between pre-hospital delay and complicated appendicitis

Subgroup	Studies	24–48 vs < 24 h		> 48 vs < 24 h	
		OR (95% CI)	Heterogeneity (P value, I^2)	OR (95% CI)	Heterogeneity (P value, I^2)
Overall	15	1.99 (1.35–2.94)	0.001, 71%	4.62 (2.99–7.13)	0.0002, 76%
Age					
Paediatric	2	1.76 (0.48–6.50)	0.01, 84%	7.37 (5.07–10.71)	0.37, 0%
Without restriction	5	1.88 (1.18–3.00)	0.03, 63%	3.26 (2.78–3.82)	0.55, 0%
Publication year					
≤ 2010	5	2.13 (1.16–3.92)	0.06, 55%	4.32 (2.11–8.88)	0.01, 68%
> 2010	3	1.82 (0.99–2.32)	0.001, 86%	4.99 (2.51–9.92)	0.0003, 87%
Study design					
Prospective	3	1.29 (0.76–2.20)	0.31, 14%	6.24 (2.20–17.66)	0.02, 76%
Retrospective	5	2.39 (1.45–3.94)	< 0.0009, 79%	4.09 (2.44–6.85)	0.001, 78%
Study centre					
Single	6	1.82 (1.17–2.83)	0.02, 63%	3.94 (2.51–6.19)	0.02, 64%
Multi	2	2.58 (1.25–5.34)	0.20, 38%	7.61 (5.18–11.19)	0.54, 0%
Setting					
USA	3	1.68 (0.65–4.34)	0.03, 72%	7.16 (5.02–10.20)	0.59, 0%
Europe	1	1.23 (0.67–2.24)	NA	2.95 (1.45–5.98)	NA
Asia	4	2.40 (1.29–4.46)	0.02, 70%	4.13 (2.08–8.19)	0.005, 77%
Perforation at admission excluded					
Yes	1	3.16 (2.23–4.49)	NA	7.69 (5.28–12.00)	NA
No	7	1.78 (1.19–2.66)	0.04, 56%	4.05 (2.68–6.12)	0.02, 59%
Complicate appendicitis					
Perforated	3	2.05 (1.14–3.67)	0.003, 83%	5.08 (2.47–10.42)	0.0003, 87%
Gangrenous, perforated	4	1.90 (0.97–3.72)	0.02, 66%	4.29 (2.15–8.54)	0.01, 68%
Cases					
≤ 500	6	1.82 (1.01–3.29)	0.03, 59%	4.44 (2.47–8.01)	0.03, 61%
> 500	2	2.21 (1.13–4.32)	0.0007, 91%	4.99 (2.08–11.97)	< 0.00001, 94%
NOS score					
≥ 7	6	2.18 (1.42–3.34)	0.0007, 76%	5.09 (3.12–8.31)	0.001, 80%
< 7	2	1.11 (0.48–2.57)	0.31, 2%	2.71 (0.65–11.33)	0.09, 66%
Symptom onset record accuracy					
Accurate	5	1.90 (1.24–2.91)	0.008, 71%	5.57 (3.05–10.17)	< 0.00001, 84%
Less accurate	3	2.02 (0.68–2.98)	0.02, 73%	3.37 (1.80–6.29)	0.23, 33%

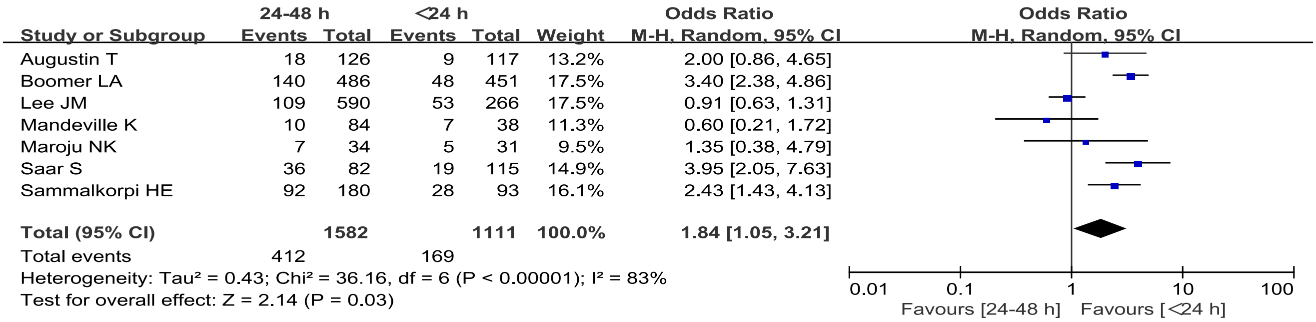
OR odds ratio, *CI* confidence interval, *NA* not available

The two funnel plots of the meta-analysis showed evidence of bias, thereby suggesting the possibility of small-study effects.

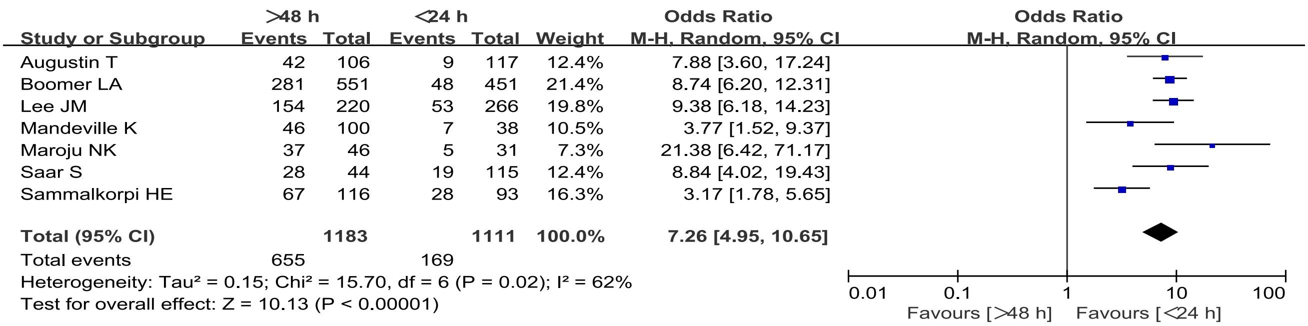
Discussion

This systematic review and meta-analysis aimed to examine the association between delay of appendectomy and risk of complicated appendicitis and post-operative SSI, which was the second meta-analysis on this subject. The first work was done by Bhangu A et al. in 2014 but that meta-analysis only focused on in-hospital delay, and the researchers concluded that short delays of less than 24 h before appendectomy were not associated with increased rates of complex pathology in selected patients.[40] Over the next few years, several new studies with contradictory results were published worldwide. Thus, it was necessary to summarize the studies on the effect of time delays for operation in patients with acute appendicitis.

We found evidence of an increased risk of complicated appendicitis in patients with longer pre-hospital and total delay. Patients in the 24–48 h category had 1.99- and 1.84-fold ($p < 0.05$) higher odds of developing complicated appendicitis, compared to patients in the < 24 h category for pre-hospital



(a) 24–48 h VS <24 h



(b) >48 h VS <24 h

Fig. 5 Results and the forest plot from the main meta-analysis of studies on association between total delay and complicated appendicitis. M-H indicates Mantel-Haenszel method. **a** 24–48 vs < 24 h. **b** > 48 vs < 24 h

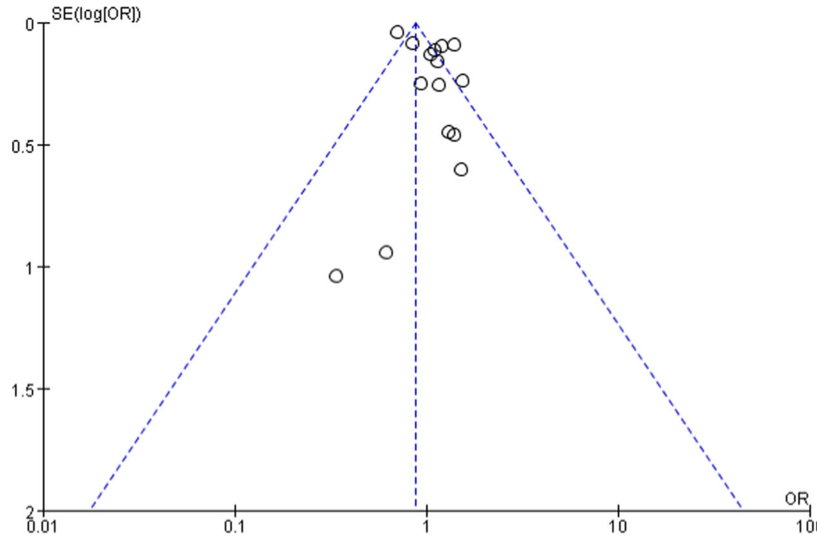
delay and total delay, respectively. However, the odds of risk declined to no significant difference in majority subgroup analysis in regard to total delay. Therefore, 24/48 h symptom duration before appendectomy will not make the patient prone to perforation, especially when antibiotic therapy was given to all patients when a diagnosis of appendicitis was established

Table 5 Subgroup analyses of studies on association between total delay and complicated appendicitis

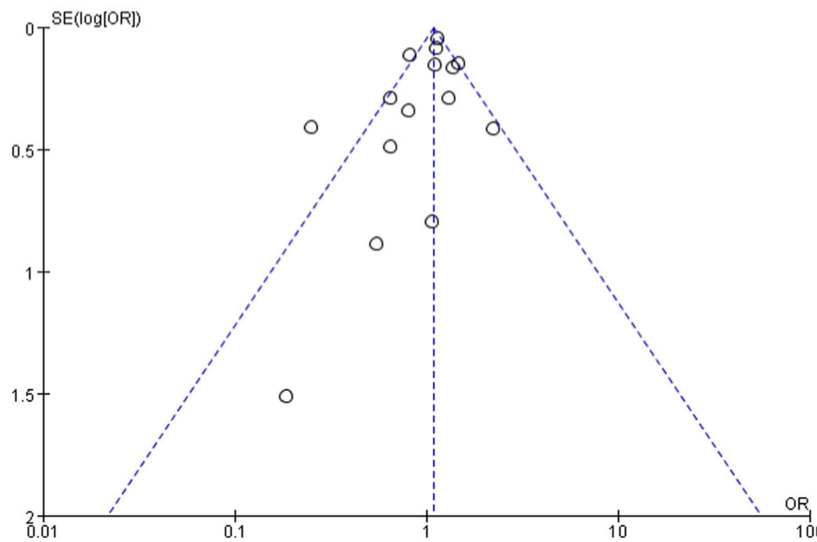
Subgroup	Studies	24–48 vs < 24 h		> 48 vs < 24 h	
		OR (95% CI)	Heterogeneity (P value, I^2)	OR (95% CI)	Heterogeneity (P value, I^2)
Overall	15	1.84 (1.05–3.21)	< 0.00001, 83%	7.57 (6.14–9.35)	0.02, 62%
Age					
Paediatric	2	1.53 (0.28–8.36)	0.002, 89%	7.87 (5.71–10.84)	0.09, 65%
Adult	3	2.71 (1.69–4.34)	0.27, 23%	5.54 (3.63–8.48)	0.007, 80%
No restriction	2	1.23 (0.58–2.59)	0.09, 64%	8.98 (6.21–12.99)	0.70, 0%
Study design					
Prospective	4	1.87 (0.91–3.87)	0.02, 69%	5.13 (3.49–7.55)	0.02, 71%
Retrospective	3	1.83 (0.70–4.77)	< 0.00001, 92%	8.84 (6.87–11.37)	0.92, 0%
Setting					
USA	3	1.77 (0.69–4.54)	0.007, 80%	7.87 (5.85–10.59)	0.24, 30%
Europe	2	2.98 (1.86–4.77)	0.26, 22%	4.45 (2.80–7.07)	0.04, 76%
Asia	2	0.94 (0.66–1.33)	0.34, 0%	10.28 (6.94–15.22)	0.20, 38%
Cases					
≤ 500	4	1.72 (0.76–3.90)	0.02, 68%	8.07 (4.45–14.62)	0.15, 43%
> 500	3	1.95 (0.82–4.62)	< 0.00001, 92%	6.65 (3.74–11.81)	0.005, 81%
NOS score					
≥ 7	4	2.58 (1.80–3.69)	0.39, 1%	7.46 (3.54–15.70)	0.02, 71%
< 7	3	1.31 (0.44–3.83)	< 0.00001, 93%	8.05 (5.63–11.51)	0.19, 39%

OR odds ratio, *CI* confidence interval

Fig. 6 Funnel plots to assess publication bias for outcomes of association between in-hospital delay and complicated appendicitis. **a** 6–12 vs < 6 h. **b** > 12 vs < 6 h



(a) 6–12 h VS <6 h



(b) >12 h VS <6 h

in the hospital. Pre-hospital delay appeared to play a more important role in the course of appendicitis. When delay time extended to more than 48 h, the odds of risk increased 4.62- and 7.57-fold ($p < 0.05$). The observation that risk estimate was similar to the main meta-analysis in subgroup analysis confirmed the strength of our findings. The heterogeneity declines in some subgroup analyses while remaining high in other subgroup analysis (Tables 4 and 5), suggesting that the heterogeneity in the meta-analysis was unable to be thoroughly explained by subgroup analyses. However, the risk estimates of all meta-analyses and the results of all individual studies consistently support the conclusion, so whether meta-regression analyses are conducted or not is no longer important.

Regarding in-hospital delay, the results of this systematic review and meta-analysis showed that the risk of developing complicated appendicitis was not increased when appendectomy was delayed 6–12 h or > 12 h after admission. The outcomes remained the same in the subgroup analysis. The results showed an interesting phenomenon that a 6–12- and > 12-h delay of appendectomy after admission is safe, but the risk of perforation increased when symptom duration exceeded 24 h before admission. A possible explanation is that once a diagnosis of acute appendicitis is established in hospital, antibiotics will be immediately administered for all patients, which may slow down the pathological progression of the appendix, such that appendectomy is sometimes no longer necessary.[43] However, the risk of developing postoperative SSI was slightly increased; the pooled OR was 1.40 (95% CI 1.11–1.77, $p = 0.004$) for a 6–12-h delay, which revealed that although antibiotic treatment can slow down the pathological progression of the appendix, the inflammatory process is still developing. However, the significance disappeared when comparing the > 12 h and < 6 h categories (OR 2.47, 95% CI 0.44–13.87, $p = 0.31$); this may be explained by the observation that a > 12-h delayed appendectomy is always planned by surgeons for particular patients in stable condition.

Since the 1880s, when Fitz and McBurney described emergency appendectomy, the exact mechanism of acute appendicitis has remained unclear. A traditional pathophysiological model takes luminal obstruction of the appendix as the major cause.[41] Obstruction of the appendiceal lumen contributes to inflammation and infection, leading to increasing tension in the wall, which can reduce blood flow and result in necrosis and perforations. An analysis performed by Andersson in 2007 showed that not all acute appendicitis cases progress to perforation and that spontaneous resolution may be a common event.[42] Based on this idea, and with the progress of antibiotic therapy, non-operative management has been suggested and practised for patients with uncomplicated appendicitis.[43] In addition, it was demonstrated to be safe to delay operation on uncomplicated acute appendicitis cases that present after hours until the next morning to avoid disrupting operating room schedules and to reduce technical errors associated with sleep deprivation and fatigue.[12,13] According to these findings, the consensus from the 2015 meeting of the European Association of Endoscopic Surgery recommended that short, in-hospital surgical delay up to 12/24 h is safe in uncomplicated acute appendicitis and does not increase complications and/or perforation rate.[44] The results of our meta-analysis also showed that in-hospital delay did not increase the complicated appendicitis rate, but with a slightly increased post-operative SSI.

However, there have some pitfalls in these studies that limit the application of their results, also leading to several drawbacks of our review. An obvious mistake is to report the differences in the proportion of perforation or morbidity between groups with short and long delay regardless of the bias in the characteristics of patients.[45] Patients with severe manifestations may be operated on soon after admission, while appendectomy will be intentionally delayed in patients with a mild infection. Second, most of the included studies did not provide the risk estimates controlling for other variables such as age and comorbidity that may play an important role in the pathological progression of acute appendicitis. Although subgroup analysis decreased the heterogeneity, we cannot fully exclude unknown or residual confounding factors that may have influence our findings. Third, several studies were excluded because of a time cut-off inconsistent with ours; although the numbers were small, the bias did exist. Finally, the large majority of the studies included in this meta-analysis were retrospective in nature, whose data were collected indirectly. These data are prone to recall bias.

Our results find a significant association between total delay and increasing complicated appendicitis incidence. A recent body of literature suggests that delaying appendectomy does not result in increased morbidity and that appendicitis could be managed as a semi-elective condition.[16–18,38] Some authors proposed that there may be two distinct forms of appendicitis: the first is a mild, simple appendicitis that responds to antibiotics or could be even self-limiting, whereas the other often seems to perforate before the patient reaches the hospital, [46] and non-operative treatment for uncomplicated appendicitis was tested in many studies.[43,47,48] At present, there is no excellent way to judge which acute appendicitis patients will respond to antibiotics or resolve spontaneously. Conservative treatment may cause a high risk of recurrence, which may be troublesome in the elderly or pregnant women, not to mention the financial burden resulting from repeated treatment. Thus, there is no help to determine how long of a delay for an appendectomy is safe, but it will be useful to determine and avoid the contributors that can cause delay in patients with acute appendicitis. The implementation of the acute surgical unit (ASU) model was proved to have an advantage in dealing with patients with acute appendicitis.[49]

Conclusion

In summary, findings from this meta-analysis provide evidence that the complicated appendicitis incidence was associated with overall elapsed time from symptom onset to admission or operation; short appendectomy in-hospital delay did not increase the risk of complicated appendicitis but was associated with a slightly increased risk of SSI. Prompt surgical intervention is warranted to relieve pain, avoid additional morbidity, enable quicker recovery and decrease costs in this population.

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Authors' Contributions Jian Li and Run Xu designed the study. Jian Li was directly involved in the full implementation of this study and was a major contributor in writing the manuscript. Deng-Min Hu, Yao Zhang, and Jian Li were jointly involved in studies collection, quality assessment, and data extraction. Tu-Ping Gong, Xue-Lian Wu, and Jian Li provided substantial contributions to the data analysis. All authors read and approved the final manuscript.

Compliance with Ethical Standards

Competing Interests The authors declare that they have no competing interests.

Ethics Statement This systematic review and meta-analysis accomplished all of the ethics requirements according to the Helsinki declaration and all international statements.

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