Systematic review

Meta-analysis of in-hospital delay before surgery as a risk factor for complications in patients with acute appendicitis

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Background: **The traditional fear that every case of acute appendicitis will eventually perforate has led to the generally accepted emergency appendicectomy with minimized delay. However, emergency and thereby sometimes night-time surgery is associated with several drawbacks, whereas the consequences of surgery after limited delay are unclear. This systematic review aimed to assess in-hospital delay before surgery as risk factor for complicated appendicitis and postoperative morbidity in patients with acute appendicitis.**

Methods: **PubMed and EMBASE were searched from 1990 to 2016 for studies including patients who underwent appendicectomy for acute appendicitis, reported in two or more predefined time intervals. The primary outcome measure was complicated appendicitis after surgery (perforated or gangrenous appendicitis); other outcomes were postoperative surgical-site infection and morbidity. Adjusted odds ratios (ORs) were pooled using forest plots if possible. Unadjusted data were pooled using generalized linear mixed models.**

Results: **Forty-five studies with 152 314 patients were included. Pooled adjusted ORs revealed no significantly higher risk for complicated appendicitis when appendicectomy was delayed for 7–12 or 13–24 h (OR 1·07, 95 per cent c.i. 0·98 to 1·17, and OR 1·09, 0·95 to 1·24, respectively). Meta-analysis of unadjusted data supported these findings by yielding no increased risk for complicated appendicitis or postoperative complications with a delay of 24–48 h.**

Conclusion: **This meta-analysis demonstrates that delaying appendicectomy for presumed uncomplicated appendicitis for up to 24 h after admission does not appear to be a risk factor for complicated appendicitis, postoperative surgical-site infection or morbidity. Delaying appendicectomy for up to 24 h may be an acceptable alternative for patients with no preoperative signs of complicated appendicitis.**

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Introduction

Acute appendicitis is a common cause of acute abdomen, with an estimated lifetime risk of 7–8 per cent worldwide[1,2]. Emergency appendicectomy is the standard of care in the treatment of acute appendicitis. Traditionally, it was thought that every unperforated appendicitis would evolve to perforated appendicitis. Fear of the development of perforated appendicitis while delaying appendicectomy has led to the widely accepted emergency appendicectomy with minimized delay. However, this fear originates from more than 100 years ago, when perforated appendicitis had very high mortality rates; this rate has decreased greatly since then[3].

Emergency surgery, and thus sometimes night-time surgery, is associated with several potential downsides. Some studies[4–7] have reported higher morbidity and error rates when working or operating at night. Other studies[8–10] focusing on this effect in patients undergoing appendicectomy have not reported higher morbidity rates. In current practice, not all hospitals are staffed or set up for 24-h operating room availability, and might not have optimal imaging modalities at their disposal at night. Furthermore, delaying appendicectomy creates more time for diagnostic tests to confirm the clinical diagnosis or, when appropriate, the opportunity for conservative treatment with antibiotics. These factors in daily practice urge guidelines to advise whether an appendicectomy can be

delayed without consequences or whether hospitals should adapt to a full 24-h diagnostic and surgical service.

The consequences of delaying an appendicectomy for acute appendicitis, in particular potential perforation of the appendix during that delay, are not clear. Perforated appendicitis might be a different disease entity from non-perforated appendicitis, rather than being the next stage of the natural disease course. Therefore, the disease itself may lead to perforation instead of the delay in treatment. This implies that most appendices will already be perforated on arrival at hospital, and perforation can thus no longer be prevented by prompt surgery. In addition, delaying surgery for acute appendicitis is not completely new: studies on antibiotic treatment of uncomplicated appendicitis involve treating these patients conservatively, operating only when this conservative treatment fails. These studies have shown that the uncomplicated subgroup may not suffer from an increased complication rate when appendicectomy is delayed, illustrated by a 10·8 per cent perforation rate in patients who had appendicectomy after 'failed' antibiotic treatment compared with a 17·9 per cent rate in patients who underwent appendicectomy immediately after randomization[11].

An earlier systematic review and meta-analysis[12] on the effect of in-hospital delay included only studies that used a 12-h cut-off time. The various cut-off times used in many other published studies have potentially caused valuable loss of information. Furthermore, only crude data were used in that review[12]. As the timing of surgery is probably influenced by patient and clinical characteristics, and clinically ill patients are likely to be operated on earlier, unadjusted data probably result in biased outcomes and may miss the true effect of the delay.

The aim of this systematic review was to assess in-hospital delay, using crude as well as adjusted data, as a potential risk factor for complicated appendicitis, surgical-site infection (SSI) and postoperative morbidity in patients with acute appendicitis.

Methods

Study identification

Two authors independently searched PubMed and EMBASE databases with the following search terms: appendicitis, appendectomy, appendicectomy, surgical procedures, surgery, operation, time-to-treatment, timing, time, early, delay, prompt and immediate (*Appendix S1*, supporting information). A clinical librarian was consulted on the search strategy. No language limit was applied. When articles were published in a language not familiar to one of the authors, a translator was consulted. The search was limited to dates later than 1990, and the last search was performed in July 2016. When full text was not available or presented results were incomplete, the corresponding author was contacted. Reference lists of obtained articles were reviewed for any omitted studies. Where there was overlap in patient cohorts of two studies, the most recent and largest study was included in the systematic review. If patient cohorts of two studies overlapped but different outcome measures were reported, both studies were included in the review. Meta-analysis Of Observational Studies in Epidemiology (MOOSE)[13] and PRISMA[14] guidelines for reporting were followed. A review protocol for this meta-analysis was not published or registered before the study was undertaken.

Study selection

Eligible prospective and retrospective studies should compare at least two time intervals of in-hospital delay in patients with acute appendicitis. A prospective cohort study was defined by data collection after the idea for the study was developed, and a retrospective cohort study was defined by data collection before the idea for the study was developed. Letters, reviews, comments, case reports and patient cohorts of fewer than ten patients were excluded, as were: studies that analysed patients treated without surgery from which the data of interest could not be analysed separately; studies that analysed patients with pathology other than acute appendicitis from which the data of interest could not be analysed separately; studies that did not define in-hospital delay; studies that included only a graphical display in figures or graphs without absolute numbers; studies that reported the number of patients in only one group of the outcome variables (for example, only the number of patients with uncomplicated appendicitis but not the total number of patients or number with complicated appendicitis); studies that did not clearly define the boundaries of time intervals; studies that reported only percentages instead of absolute numbers or odds ratios (ORs); abstracts and conference proceedings; and animal or laboratory studies. The two reviewers independently considered all studies retrieved from the search for eligibility against these criteria. Any disagreements were resolved through discussion.

Quality assessment

The two reviewers critically appraised each study using the Newcastle–Ottawa Scale, an eight-item scoring system that is reliable and valid in the quality assessment of observational cohort studies in systematic reviews[15]. Any disagreements were resolved through discussion. The level

of evidence was applied according to the GRADE criteria[16] and reported.

Data extraction

The two reviewers independently reviewed each included article. Each extracted the data on a predefined evidence table, after which the two tables were compared. Any disagreements were resolved through discussion. Data collected for each article included: study design (retrospective or prospective cohort) and setting (country and number of hospitals); age and number of patients; definitions of delay (start of delay at emergency department presentation, hospital admission or diagnosis) and complicated appendicitis (perforation or perforation and gangrene combined); diagnostic modality for complicated appendicitis (surgery, pathology or both); negative appendicectomies included or excluded; outcome measures reported; timing categories reported; absolute numbers or OR for outcome measure; confounders that ORs were adjusted for.

Outcome measures

The primary outcome measure was complicated appendicitis (perforation or gangrene, as reported by individual studies) after appendicectomy for acute appendicitis within different time intervals of in-hospital delay. Other outcome measures included postoperative complications: wound infection and postoperative intra-abdominal abscess separately and combined; and postoperative morbidity. Outcomes were reported as adjusted data (adjusted for the fact that an appendix might already be perforated at arrival in the hospital and could therefore no longer perforate due to delayed treatment) and unadjusted data. Adjusted and unadjusted data were analysed in two meta-analyses separately, each with their own specific statistical methods.

Statistical analysis

For adjusted data, a random-effects model (DerSimonian and Laird) was used to calculate the pooled adjusted ORs and confidence intervals. Statistical heterogeneity was assessed using χ^2 and I^2 analyses. Statistical analyses for the adjusted ORs were conducted using Review Manager version 5·3, 2014 (The Cochrane Collaboration, The Nordic Cochrane Centre, Copenhagen, Denmark).

For unadjusted data, a generalized linear mixed model was fitted to be able to meta-analyse all different time intervals from various studies for each outcome measure. Odds were calculated from the crude data provided by the studies. Those odds accounted for the time interval used by the study, but were converted to odds for each individual hour that was entered into the model. The odds for each hour was the dependent variable in the generalized linear mixed model. The in-hospital delays in hours were the repeated measures and were entered as a fixed effect into the model. The odds in each hour were weighted by the number of patients per hour. This amount was calculated by dividing the total number of patients in a time interval by the duration of that interval. Subsequently, estimated mean odds were calculated by the model and visualized in a graph. The mean odds of newly created time intervals of interest (such as delay of 13–24 h *versus* surgery within 12 h) were converted into ORs.

A sensitivity analysis was performed to identify potential subgroups of prespecified study characteristics that resulted in different effects of in-hospital delay. This analysis shows study characteristics that are positively or negatively associated with the baseline risk for complicated appendicitis when treatment is delayed. The univariable and multivariable (including all study characteristics) pooled coefficients of studies with that specific study characteristic were divided by the pooled coefficients of the other studies together, creating an OR. An OR greater than 1 indicates a larger association; a ratio lower than 1 indicates a smaller association. Because data were generated by applying the odds for the entire interval to each hour separately, statistical significance (*P* values) were no longer trustworthy and are therefore not reported in the analyses of unadjusted data.

An in-depth clarification of the statistical analysis of unadjusted data is given in *Appendix S2* (supporting information). Statistical analysis of the unadjusted data was conducted using SPSS® version 23·0 (IBM, Armonk, New York, USA).

Results

Systematic review

The search retrieved 6128 records. After removal of duplicates, 4643 records remained. Based on title and abstract, 4448 articles were excluded. A total of 195 full-text articles were assessed for eligibility. Screening with the predefined criteria resulted in 45 articles that were included in the review; 150 articles were excluded (*Fig. 1*). *Table S1* (supporting information) lists the 150 articles excluded based on full-text review, with reasons for exclusion.

Study characteristics

No RCTs were found. All studies were observational; 40 were retrospective and five were prospective cohort studies. Two-thirds of the studies were published in or after 2010.

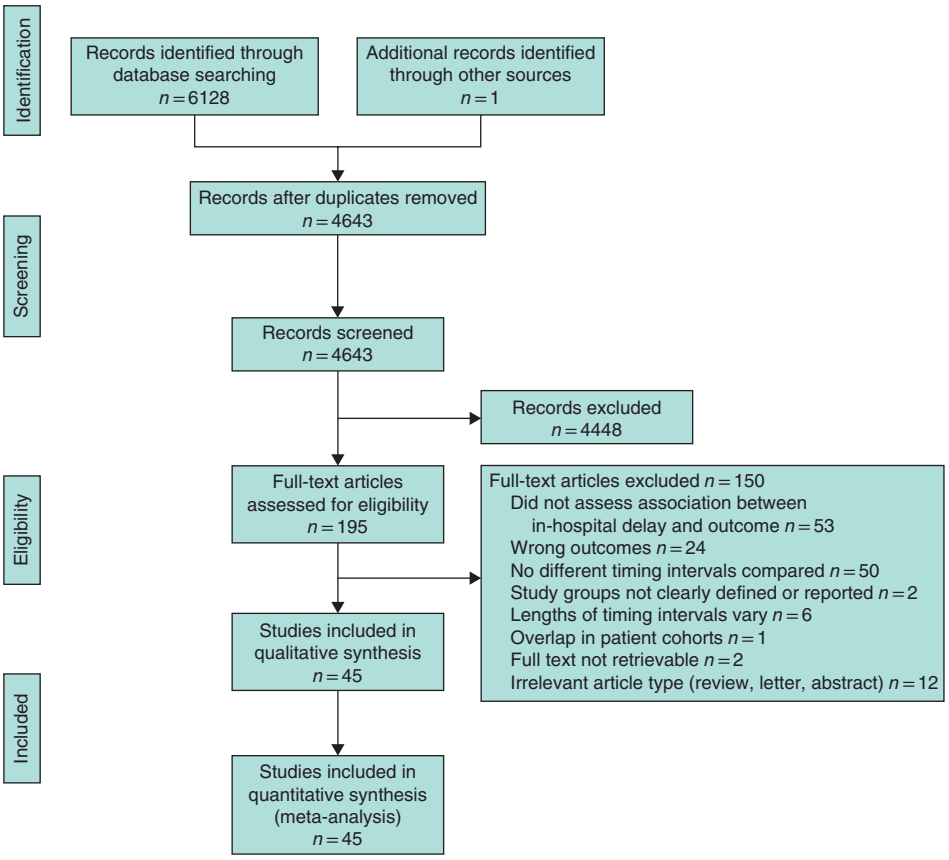

Fig. 1 PRISMA flow diagram for the study

Seven studies[17–23] analysed only children under the age of 18 years; the other 38 studies analysed adults alone or children and adults combined.

The beginning of in-hospital delay was defined as arrival or physical examination in the emergency department in 22 studies, as clinical or radiological diagnosis in seven studies, and as hospital admission in 14 studies. In 40 studies[12,17–55] complicated appendicitis was a reported outcome measure, 19 studies[12,17,19,20,23,25–29,31,35,37,41,50,54–57] reported SSI, 19[17,20,23,25,27,29,35–37,39,41,43,47,50,54–58] reported wound infection, 16[17,20,23,25,27,29,35,37,39,41,50,52,54–57] reported postoperative intra-abdominal abscess and 15 studies[12,23,25,28,31,35,39,40,44,49,54,56,57,59,60] reported postoperative morbidity as an outcome measure.

Complicated appendicitis was defined solely as perforated appendicitis in 29 studies and as perforated or gangrenous appendicitis in 11. Perforation appeared to include appendicular abscess in most studies, but a few explicitly reported the definition of perforation in such detail. Study characteristics are summarized in *Table S2* (supporting information).

Population characteristics

A total of 152 314 patients were included in this review, distributed for outcome to complicated appendicitis (81 437 patients), SSI (24 067), wound infection (20 709), postoperative intra-abdominal abscess (20 350) and postoperative morbidity (114 505). In the 45 studies, 48 different time intervals were used; 12 intervals were infinite intervals (no defined endpoint, such as 'delay longer than 12 h').

Critical appraisal

All studies were observational cohort studies (40 retrospective, 5 prospective). Therefore, risk of bias was assessed using the Newcastle–Ottawa Scale (*Table S3*, supporting information). Most studies did not apply inclusion criteria other than a confirmed diagnosis of acute appendicitis. Seven studies included only patients under the age of 18 years. As children comprise a substantial proportion of patients with acute appendicitis, all study cohorts were considered representative of patients in the community. In all

Table 1 Level of evidence according to the GRADE criteria[16]: prolonged in-hospital delay compared with immediate appendicectomy for prevention of complicated appendicitis, surgical-site infection, wound infection, postoperative intra-abdominal abscess and postoperative morbidity

			Quality assessment						
Outcome	No. of studies	No. of participants	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence*
Complicated appendicitis	40	81 437	Observational studies	Serious	Serious	Not serious	Not serious	No reason to suspect publication bias	Very low
Surgical-site infection	19	24 067	Observational studies	Serious	Serious	Not serious	Not serious	No reason to suspect publication bias	Very low
Wound infection	19	20 709	Observational studies	Serious	Serious	Not serious	Not serious	No reason to suspect publication bias	Very low
Postoperative intra-abdominal abscess	16	20 350	Observational studies	Serious	Serious	Not serious	Not serious	No reason to suspect publication bias	Very low
Postoperative morbidity	15	114 505	Observational studies	Serious	Serious	Not serious	Not serious	No reason to suspect publication bias	Very low

*Summary estimate based on the five items in previous columns.

studies the unexposed cohorts were drawn from the same hospitals and communities.

This review included only patients with a surgically or pathologically confirmed diagnosis of acute appendicitis; therefore, exposure was ascertained in all patients. All but four studies did not affirm the absence of perforation of the appendix at the start of treatment. This introduced bias for the outcome measure 'complicated appendicitis' at the time of surgery. After all, when a case of acute appendicitis is already perforated on arrival in the hospital, delaying the treatment could never result in a change of the outcome 'perforation'. Four[18,35,36,47] of 45 studies attempted to reduce this limitation by including only patients without signs of complicated appendicitis on preoperative CT.

Only studies that reported adjusted ORs gave comparability between the study groups. All other studies suffered from limited comparability because of the tendency to operate on clinically ill patients earlier. Assessment of outcome was not blinded and based on medical records in all studies. Details of the follow-up were lacking in most studies. For studies on the association between delay and rates of complicated appendicitis, this was not a major problem. All patients underwent surgery, which automatically means sufficient follow-up to verify the stage of appendicitis. However, all other outcomes (SSI and morbidity) occur during follow-up. Therefore, the lack of description of this follow-up, especially the lack of information about the differences in rates of loss to follow-up between groups, could have introduced attrition bias.

The level of evidence by GRADE was downgraded from 'low' (evidence originating from observational studies) to 'very low' due to study quality and inconsistency (*Table 1*).

Unpooled results

All crude data were entered into the model and are therefore discussed in the 'pooled results' section below. Adjusted and unadjusted ORs reported by some studies, however, could not all be pooled in the meta-analyses. Most of these unpooled studies found no significantly higher odds for all five outcome measures. In addition, all unpooled time intervals that did find a significantly higher odds concerned infinite intervals. In such intervals, the exact moment of delay from which the risk is increased is unclear. Results from, for instance, an interval 'longer than 12 h' do not show whether an increased risk accounts for patients with a delay of 13 h or whether this risk is caused mainly by patients with a much longer delay.

For the outcome 'complicated appendicitis', five studies[19–21,28,48] found no increased risk and one study[50] found an increased risk for a delay longer than 12 h

Fig. 2 Schematic illustration of data for the association between in-hospital delay and complicated appendicitis. Adjusted and unadjusted odds ratios, and crude data are shown for each 3-h increment as provided by the studies

(*Fig. 2*). Two studies[12,26] reported higher odds for SSI for a delay longer than 6 h and 48 h respectively (*Fig. S1*, supporting information). Three unpooled studies[17,29,39] found no association between delay and wound infection and postoperative intra-abdominal abscess separately (*Figs S2* and *S3*, supporting information). Finally, the odds for postoperative morbidity were not increased in two unpooled studies[39,49], but were increased in infinite

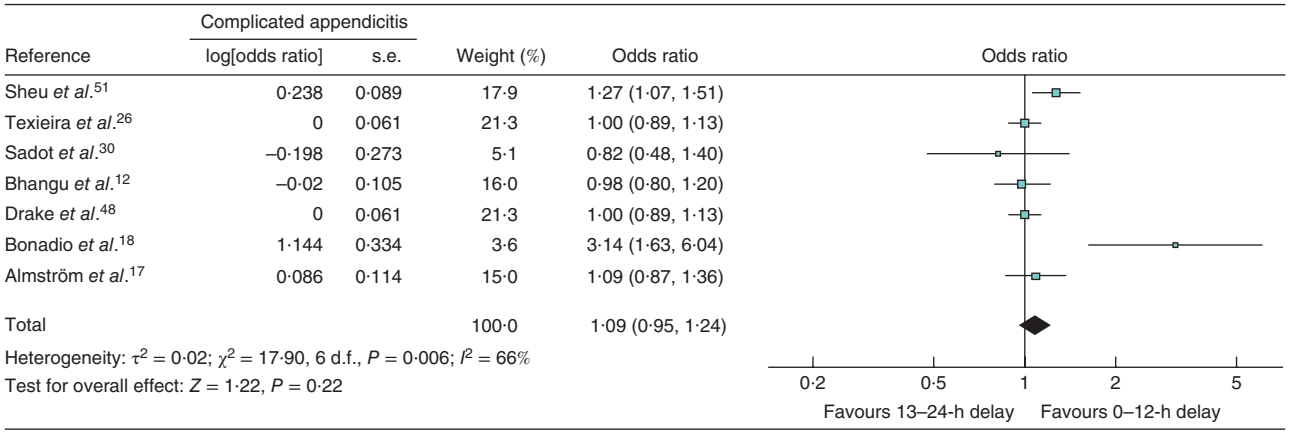

Fig. 3 Forest plot comparing adjusted odds ratios for complicated appendicitis, 13–24 *versus* 0–12 h of delay. An inverse-variance random-effects model was used for meta-analysis. Odds ratios are shown with 95 per cent confidence intervals

Table 2 Confounders that odds ratios were adjusted for

Reference	Odds ratio adjusted for:
Sheu *et al.*[51]	Age, sex, fever, leucocyte shift to the left, duration of pain before registration in ED, anorexia, migrating pain, retrocaecal appendix
Busch *et al.*[50]	Age, sex, time of admission, size of institution
Teixeira *et al.*[26]	Age, sex, leucocytosis, surgical technique (only SSI), presence of perforation (only SSI), time to operating room (only SSI)
Sadot *et al.*[30]	Age, fever, WBC, patient interval
Bhangu *et al.*[12]	Age, sex, BMI, ASA grade, time of operation, histology (only SSI and morbidity), duration of surgery (only SSI and morbidity), initial operative method (only SSI and morbidity), consultant presence in theatre (only SSI and morbidity)
Drake *et al.*[48]	Age, sex, race, ethnicity, insurance, hospital volume, hospital location
Bonadio *et al.*[18]	Age, fever, presence of appendicolith
Chen *et al.*[49]	Age, sex, leucocytosis, time from ED to appendicectomy (only morbidity), perforated appendicitis (only morbidity), open appendicectomy (only morbidity)
Fair *et al.*[60]	Sex, previous operation, any preoperative condition, current pneumonia, alcohol, minority, pregnancy, amongst 28 other medical history characteristics
Mandeville *et al.*[21]	Age, sex
Almström *et al.*[17]	Age, sex, fever, WBC, CRP, histopathology (only WI and PIAA), time of operation (only WI and PIAA)
Gurien *et al.*[20]	Age, sex, WBC, BMI, laparoscopic surgery, co-morbidity
Jeon *et al.*[39]	Age, sex, fever, leucocytosis, migration of pain, tachycardia, co-morbidity, previous abdominal surgery, time of admission, open appendicectomy, prehospital delay, presence of perforation (only WI, PIAA and morbidity)
Sauvain *et al.*[29]	Age, sex, duration of pain, Charlson score, different hospitals

ED, emergency department; SSI, surgical-site infection; WBC, white blood cell count; CRP, C-reactive protein; WI, wound infection, PIAA, postoperative intra-abdominal abscess.

intervals 'longer than 48 h' in two studies[12,60] (*Fig. S4*, supporting information).

Pooled results for complicated appendicitis

Two distinct comparisons with adjusted ORs could be made. First, delay of 7–12 h was compared with that of 0–6 h, resulting in a non-significantly higher pooled OR of 1·07 (95 per cent c.i. 0·98 to 1·17) (*Fig. S5*, supporting information). Second, a delay of 13–24 h was also not significantly associated with complicated appendicitis compared with a delay of 0–12 h (pooled OR 1·09, 0·95 to 1·24) (*Fig. 3*). Both meta-analyses had substantial heterogeneity (I^2 value of 72 and 66 per cent respectively). *Table 2* shows, per study, the confounders for which the ORs were adjusted.

The schematic illustration of the unadjusted data shows that many studies found no increased risk of complicated appendicitis when appendicectomy was delayed (*Fig. 2*). Only one study[41] found an significantly increased risk in intervals with a defined endpoint: delay of 3–6 and 6–9 h. Two studies[41,44] found an increased risk for a delay 'longer than 9 h' and 'longer than 24 h' respectively.

All 37 studies reporting crude data were entered into the generalized linear mixed model. *Fig. 4* shows the estimated mean odds and corresponding confidence intervals

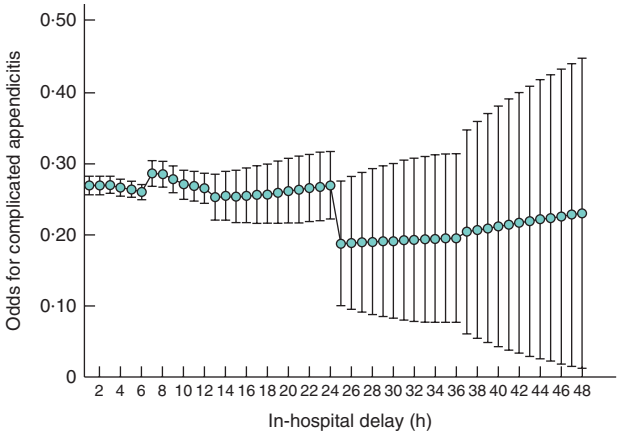

Fig. 4 Estimated mean odds with confidence intervals for the association between in-hospital delay of up to 48 h and complicated appendicitis based on a generalized linear mixed model

for complicated appendicitis when appendicectomy was delayed for up to 48 h. In the first 6 h of delay, the odds for complicated appendicitis are fairly constant. The successive hours until a 12-h delay result in somewhat higher odds, followed by somewhat decreased odds during the interval 13–24 h. This results in an estimated OR of 1·03 for the interval 7–12 h compared with 0–6 h, an estimated OR of 0·96 for 13–24 *versus* 6 h, and an estimated OR of 0·94 for 13–24 *versus* 0–12 h (*Table S4*, supporting information). As data were generated by applying the odds for the entire interval to each hour separately, confidence intervals for the estimated ORs would not be informative and so were not calculated. In addition, the confidence intervals displayed in *Fig. 4* are not trustworthy in an absolute manner. They do, however, show an increased statistical uncertainty of risk after 24 h because of fewer studies reporting results for those intervals containing a smaller number of patients.

The sensitivity analysis shows study characteristics that were positively or negatively correlated with the baseline risk for complicated appendicitis when treatment was delayed (*Table 3*). Studies that included only patients presumed before surgery to have uncomplicated appendicitis showed a decreased risk of complicated appendicitis when appendicectomy was delayed (OR 0·36). This means that patients presenting with uncomplicated appendicitis were less likely to develop complicated appendicitis when appendicectomy was delayed. Furthermore, studies that included only children showed a similar risk of developing complicated appendicitis during delay compared with that in studies with adults or with children and adults combined (OR 1·23). The inclusion or exclusion of negative appendicectomies did not influence the effect of delayed appendicectomy on the risk of complicated appendicitis (OR 0·93).

Table 3 Sensitivity analysis of studies on the association between in-hospital delay and complicated appendicitis

	No. of studies	Odds ratio	
		Univariable	Multivariable
Patient selection			
Age			
All	33	1·00 (reference)	1·00 (reference)
Age < 18 years	7	1·46	1·23
Preoperative stage included			
All	34	1·00 (reference)	1·00 (reference)
Only uncomplicated	6	0·64	0·36
Negative appendicectomies			
Excluded	36	1·00 (reference)	1·00 (reference)
Included	4	0·98	0·93
Study definitions			
Diagnostic modality*			
Histopathology	24	1·00 (reference)	1·00 (reference)
Surgery	1	1·70	1·18
Both combined	14	0·83	0·82
Definition of complicated appendicitis			
Perforation	29	1·00 (reference)	1·00 (reference)
Perforation/gangrene	11	1·47	1·28
Definition of start of delay			
Emergency department	20	1·00 (reference)	1·00 (reference)
Diagnosis	6	0·54	1·16
Admission	14	0·79	0·93

*One study missing.

Pooled results for surgical-site infection

No adjusted data were available for the outcome SSI. Unadjusted data showed that none of the studies reported a significantly higher odds of SSI when appendicectomy was delayed (*Fig. S1*, supporting information), although ten of the 18 studies did not provide information on significance. All 18 studies reporting crude data were entered in a generalized linear mixed model (*Fig. S6*, supporting information). The estimated mean odds of SSI for each hour showed a similar pattern to those for complicated appendicitis: an increase in odds from 7 to 12 h of delay followed by a decrease from 13 to 24 h. The estimated odds were lower for a delay of 13–24 h than for a delay of 0–12 h (OR 0·49). Presumably these odds are lower because most patients at risk of SSI (ill patients suffering from complicated appendicitis) were operated on earlier (*Table S4*, supporting information).

Pooled results for wound infection

No adjusted data were available for the outcome wound infection. Unadjusted data showed comparable odds for wound infection when appendicectomy was delayed for almost all time intervals. Only one infinite interval[41] showed an increased risk for a delay 'longer than 3 h' (*Fig. S2*, supporting information). Similarly, when all 18 studies reporting crude data were entered in a generalized linear mixed model, the estimated mean odds of wound infection were fairly constant for the entire 0–24-h interval (*Fig. S7*, supporting information).

Pooled results for postoperative intra-abdominal abscess

No adjusted data were available for the outcome postoperative intra-abdominal abscess. For unadjusted data, only three[25,41,50] of 15 studies reported a significantly higher odds of postoperative intra-abdominal abscess, but all three involved infinite intervals (*Fig. S3*, supporting information). The available data for this outcome measure were not suitable (too few and too heterogeneous) for a generalized linear mixed model to be fitted.

Pooled results for postoperative morbidity

No adjusted data were available for the outcome postoperative morbidity. Unadjusted data showed that only three[44,57,60] of 14 studies had significantly higher odds of postoperative morbidity, but all three related to an infinite time interval (longer than 24 or 48 h) (*Fig. S4*, supporting information). The estimated mean odds of postoperative morbidity for these 14 studies were constant during the first 24 h of delay when the crude data were entered into a generalized linear mixed model (*Fig S8*, supporting information).

Discussion

This systematic review and meta-analysis demonstrated that delayed appendicectomy for presumed uncomplicated appendicitis for up to 24 h after admission was not a risk factor for complicated appendicitis, SSI or morbidity. Meta-analyses of both the adjusted and unadjusted data support this conclusion. The sensitivity analysis showed, in particular, that in uncomplicated appendicitis there is no increased risk of complications when appendicectomy is delayed. Moreover, studies including only children showed comparable results, and thus children may not be exceptions to these conclusions.

Currently, several guidelines give no general recommendations about the timing of appendicectomy. Two guidelines[61,62] do make a recommendation on this topic, but recommendations are conflicting. Both are based on only five studies (and not even the same 5 studies) and on the meta-analysis of unadjusted data performed by Bhangu and colleagues[12]. That meta-analysis reported no significant difference in rates of complicated appendicitis when delay was less than 12 h or more than 12 h, or between less than 12 h and 12–24 h. The 2016 World Society of Emergency Surgery guideline[61] concludes that an in-hospital delay of up to 12–24 h is safe in uncomplicated appendicitis. The European Association for Endoscopic Surgery[62] also published its guideline in 2016; this states that delaying an appendicectomy increases the risk of perforated appendicitis and therefore it is recommended that appendicectomy be performed as soon as possible.

In this systematic review, limitations within the studies as well as limitations in the meta-analyses must be noted. All studies were observational cohort studies, leading to a selection bias inherent to non-randomized studies. Furthermore, there were several differences between the studies, reflected, for example, by the substantial statistical heterogeneity in the present meta-analyses of adjusted ORs. Amongst others, the method of diagnosing complicated appendicitis, definition of complicated appendicitis and the timing of the in-hospital delay were factors that varied between studies. The most important limitation was that most study results were unadjusted for confounders. As clinically ill patients are more likely to have complicated appendicitis and more likely to be operated on earlier, selection bias is an important issue. This probably explains the limited increase in odds for complications during 7–12 h of in-hospital delay, as patients who already have complicated appendicitis on arrival at the hospital 'contaminate' the group with uncomplicated appendicitis still at risk of developing perforated appendicitis. Therefore, results from the meta-analyses of adjusted ORs are most valuable. These results are adjusted for confounders that are possible predictors of complicated appendicitis on arrival at the hospital. By adjusting for these confounders, only the effect of the delay to surgery itself is analysed, and patients who already have complicated appendicitis on arrival will have limited to no influence on the analysis results. Because of the many different time intervals used in the studies, pooling the adjusted data was only partially possible. Furthermore, four of the adjusted ORs in that meta-analysis were calculated from a continuous OR per h provided by those studies. Using those ORs involved the assumption that the odds of complicated appendicitis had a linear correlation with in-hospital delay.

The majority of evidence on this topic consisted of unadjusted data, reported in nearly 50 different time intervals among the studies. Discarding all this evidence without review or meta-analysis could have led to biased results. Therefore, although meta-analysis of these data suffers from some methodological limitations, a meta-analysis was performed to assess whether this evidence showed different results compared with adjusted data. In addition, the large number of studies reporting unadjusted data allowed subgroup analyses. Several assumptions were made in the unadjusted data meta-analysis. The odds reported by the studies during a time interval were assigned to each hour individually to prevent wrongful assignment of odds to hours in newly created time intervals, which were initially not part of that time interval. Notwithstanding that this approach requires the assumption that the odds were constant during the entire interval, it is closer to reality than overlapping hours between time intervals, and provides a more detailed view of the change in odds during the hours of delay. In addition, the weight of the odds for each hour was determined by dividing the total number of patients in that interval by the duration of the interval in hours, resulting in the estimated number of patients per hour. This approach requires the assumption that patients were distributed evenly across the interval, but the odds are weighted much more precisely by this hour-specific weight than when the total number of patients is used as the weight for all intervals in that study.

For each outcome, multiple models were created to find the best possible fit. Despite different settings, the overall results remained comparable between the different models. Because the results appeared not to be influenced by changes in analysis strategies, the conclusions that can be drawn based on the models are strengthened. As data were generated by applying the odds of a time interval to each hour individually, *P* values in the sensitivity analysis were no longer trustworthy and hence not reported. Therefore, interpretation of calculated ORs could not be based on statistical significance but only on interpretation of the OR itself. There is no consensus about the level of minimal clinically importance in ORs. However, an OR of 0·36 for the risk of developing complicated appendicitis during delay in patients with appendicitis presumed to be uncomplicated before surgery (compared with that in all patients with appendicitis as a single group) would appear to indicate that these patients do not have an increased risk of developing complicated appendicitis during the treatment delay. Furthermore, an OR of 1·23 for the risk in children (compared with that in adults and children as a single group) would seem, although slightly higher, to be not clinically relevant. This would imply that the safety of delayed appendicectomy for up to 24 h may be safe in children as well.

The conclusions drawn in this study have been based mainly on the outcome measure of complicated appendicitis. This measure was reported by almost all studies and therefore provided the most reliable results. Even for this outcome measure, statistical uncertainty increased after 24 h of delay. Therefore, conclusions based on the available literature were restricted to these first 24 h. In addition, the other outcome measures – SSI and morbidity – are likely to be the consequence of complicated appendicitis. For these reasons, the sensitivity analysis was performed only for complicated appendicitis, although the results could probably be applied to other outcome measures.

A plausible explanation for the finding that delaying appendicectomy for uncomplicated appendicitis appeared to be without repercussions is that uncomplicated and complicated appendicitis are different disease entities with a distinct pathophysiology. Apart from the findings of this systematic review, several earlier findings support this line of thought. An epidemiological study[63] found a 25-year decline in the incidence of unperforated appendicitis until 1995, followed by an increased incidence after the introduction of CT and laparoscopic appendicectomy. Nonetheless, the number of cases of perforated appendicitis followed a completely different trend and slowly increased over time. A Swedish study[64] of over 56 000 patients from seven population-based studies found that a lower threshold for surgery resulted in a higher number of negative appendicectomies, although the number of patients operated on with perforated appendicitis remained the same. Thus, lowering the threshold for surgery does not prevent ruptured appendix, but merely increases the percentage of negative appendicectomies and uncomplicated appendices removed. In a scenario without this lowered threshold for surgery, some patients now diagnosed with uncomplicated appendicitis would have had resolution without diagnosis. Similar findings were reported by two other studies[65,66]: a lower proportion of uncomplicated appendicitis cases and negative appendectomies in patients treated expectantly compared with those following a more aggressive approach and earlier surgery. Additionally, age does not affect the incidence of perforated appendicitis; it only strongly affects the incidence of non-perforated appendicitis[64]. Thus, the greater proportion of perforations is not caused by a higher number of perforations but by a lower rate of non-perforated appendicitis. Only the proportion of perforations changes, depending on the number of cases of non-perforated appendicitis that remain undiagnosed and resolve spontaneously. In addition, the higher proportion of perforations with longer symptom

durations reported by earlier studies was possibly not caused by an increase in perforations but by a decrease in non-perforated appendicitis[67].

Therefore, the traditional belief of increasing numbers of perforations during the course of appendicitis seems not to be true. Most cases of appendicitis probably rupture at an early stage. Thus, only a few perforations could be prevented by very early surgery after the onset of symptoms and arrival at the hospital.

Biological studies have found different inflammatory markers in uncomplicated appendicitis than in complicated appendicitis. This suggests a genetically determined difference in immune activation between uncomplicated and complicated appendicitis, and that perforation might be caused by immune-mediated tissue destruction via an exaggerated immune response rather than by delaying appendicectomy[68–70].

As well as their importance in the surgical treatment of acute appendicitis, the results of the present meta-analysis concur with reports of the safety of initial conservative treatment with antibiotics for uncomplicated appendicitis[11]. In studies on antibiotic treatment of uncomplicated appendicitis, conservative treatment with antibiotics is started and appendicectomy is performed if conservative treatment fails after 24–48 h[11]. After selection of patients suitable for antibiotic treatment, perforation rates found during this delayed surgery are very low. A recent meta-analysis[11] of five RCTs found a perforation rate after 'failed' antibiotic treatment of only 10·8 per cent.

With consideration given to the methodological limitations of the included studies, results adjusted for the fact that an appendix may already be perforated on arrival at hospital, and that delayed treatment could therefore never cause perforation, showed a comparable risk of complicated appendicitis when treatment was delayed for 13–24 h compared with surgery within 12 h (OR 1·09, 95 per cent c.i. 0·95 to 1·24). Explorative meta-analysis of the unadjusted data supported this finding, and sensitivity analysis showed that patients presumed to have uncomplicated appendicitis before surgery did not have an increased risk of developing complicated appendicitis during a delay. After this 24-h time period, the uncertainty of results in the literature is too large to draw any firm conclusions. However, future studies on antibiotic treatment of uncomplicated appendicitis may provide valuable information on the safety of a delay longer than 24 h. For patients with clinical or radiological signs of complicated appendicitis, delaying surgical treatment is not advocated. In addition, appendicectomy should not be delayed unnecessarily to minimize the discomfort of patients, but a delay of up to 24 h seems to be safe when there are reasons for delay.

Disclosure

The authors declare no conflict of interest.

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Supporting information

Additional supporting information can be found online in the Supporting Information section at the end of the article.