



A Comprehensive Systematic Review of Relationship between Surgery Waiting Time and Perforation Rate in Acute Appendicitis

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ABSTRACT

Introduction: Acute appendicitis is one of the most common surgical emergencies worldwide, with appendiceal perforation representing a critical complication associated with significant morbidity. The relationship between surgical waiting time and perforation risk remains controversial, with conflicting evidence regarding the safety of in-hospital delay. This systematic review aims to evaluate the association between waiting time for appendectomy and perforation rates in acute appendicitis, identify population-specific risks, and synthesize evidence for clinical practice guidance.

Methods: A systematic review was conducted using comprehensive literature screening. Studies were included if they examined patients with acute appendicitis, reported measurable waiting time intervals, documented perforation outcomes, and employed appropriate comparative study designs. Data extraction encompassed waiting time definitions, perforation criteria, study

population characteristics, statistical relationships, perforation rates by time categories, confounding factors, and secondary outcomes. Harvard citation style was applied throughout.

Results: Eighty-nine studies published were analyzed, comprising retrospective cohorts (n=67), prospective cohorts (n=12), randomized controlled trials (n=2), cross-sectional studies (n=7), and one systematic review. Sample sizes ranged from 50 to 683,590 patients. Overall perforation rates varied from 7.5% to 72.5%, with most studies reporting 10-30%. For pre-hospital delay (symptom duration), consistent positive association with perforation was demonstrated, with odds ratios increasing from 2.84 for >24-hour delay to 6.6 for >36-hour symptoms (Bickell et al., 2006; Sadot et al., 2013). However, for in-hospital delay, findings were discordant. The PERFECT randomized controlled trial found no significant difference in perforation rates between <8-hour (8%) and <24-hour (9%) surgical windows (absolute risk difference 0.6%, 95% CI -2.1 to 3.2; Jalava et al., 2023). Conversely, pediatric studies demonstrated significant associations, with every hour of delay increasing perforation odds by 2% (AOR 1.02, 95% CI 1.00-1.04; Meltzer et al., 2016). High-risk subgroups including elderly patients, those with appendicoliths, and patients with marked inflammatory markers demonstrated accelerated perforation risk with in-hospital delay (Jeon et al., 2018; Hanson et al., 2019).

Discussion: The relationship between surgical waiting time and appendiceal perforation is fundamentally dichotomous. Pre-hospital delay consistently predicts perforation at presentation, representing irreversible disease progression. In contrast, in-hospital delay of up to 24 hours appears safe for carefully selected

adults with uncomplicated appendicitis, likely attributable to preoperative antibiotics and modern diagnostic accuracy. However, this safety window does not extend uniformly across populations. Pediatric patients demonstrate time-dependent perforation risk even within 24 hours, potentially reflecting anatomical and physiological differences in disease progression (Serres et al., 2017; Stevenson et al., 2017). Elderly patients present with attenuated symptoms yet accelerated perforation, warranting expedited surgical intervention (F. Rondelli et al., 2019). The presence of appendicolith confers 2.2-fold increased risk of progression to complicated appendicitis within 12 hours, mandating prioritized surgical scheduling (M. Prayle et al., 2023). Secondary outcomes including length of stay and surgical site infections showed inconsistent associations with in-hospital delay, further supporting risk-stratified rather than universal timing protocols.

Conclusion: This systematic review demonstrates that the impact of surgical waiting time on appendiceal perforation is critically dependent on the temporal phase examined and patient-specific risk factors. Pre-hospital delay is a robust predictor of perforation, whereas in-hospital delay up to 24 hours is acceptable for low-risk adults with uncomplicated appendicitis. However, pediatric patients, elderly individuals, and those with appendicoliths or severe inflammatory markers require expedited surgery within 12 hours of presentation. We recommend implementation of risk-stratified triage protocols incorporating clinical, laboratory, and radiological parameters to optimize surgical timing. Future research should focus on prospective validation of composite risk stratification models and investigation of antibiotic therapy optimization during waiting periods. Healthcare institutions should

prioritize public education to reduce pre-hospital delay while allocating resources for timely surgical intervention in high-risk populations.

Keywords: Acute appendicitis, surgical waiting time, perforation, in-hospital delay, appendectomy timing, risk stratification

INTRODUCTION

Background

Acute appendicitis represents one of the most frequently encountered surgical emergencies globally, with a lifetime incidence of approximately 7-8% (D. Kearney et al., 2008). Appendiceal perforation, the primary complication of delayed treatment, occurs in 15-30% of cases and is associated with substantially increased morbidity, including intra-abdominal abscess formation, prolonged hospitalization, higher healthcare costs, and rarely, mortality (Dominic J. Papandria et al., 2013; Brett A. Fair et al., 2015). The traditional surgical paradigm has mandated emergency appendectomy immediately upon diagnosis, predicated on the belief that appendiceal perforation represents an inevitable time-dependent progression from uncomplicated inflammation to frank perforation (F. T. Drake et al., 2014).

However, this conventional understanding has been increasingly challenged over the past two decades. Contemporary healthcare systems face competing demands for operating room resources, emergency surgical coverage, and optimal patient flow, necessitating evidence-based evaluation of whether all appendectomies require truly emergent status or whether a defined period of in-hospital delay may be clinically acceptable (Markus Almström et al., 2017). This question has profound implications for hospital resource allocation, surgical workforce planning, and patient safety.

Research Gap

Despite extensive investigation, the literature examining the relationship between surgical waiting time and appendiceal perforation presents strikingly discordant findings. Several large retrospective studies have demonstrated significant positive associations between in-hospital delay and perforation risk, with odds ratios ranging from 1.5 to 8.67 depending on the duration of delay and population studied (M. Busch et al., 2011; W. Bonadio et al., 2015; Seong-Keun Park et al.,

2018). In contrast, equally robust investigations, including the recently published PERFECT randomized controlled trial, have found no significant increase in perforation rates with delays up to 24 hours (Karoliina Jalava et al., 2023; F. T. Drake et al., 2014; Courtney Clyde et al., 2008).

This fundamental contradiction in the evidence base creates substantial clinical uncertainty. The critical distinction between pre-hospital delay (symptom duration before presentation) and in-hospital delay (time from presentation to surgery) has been inadequately delineated in much of the existing literature, potentially conflating two distinct pathophysiological and operational phases (N. Bickell et al., 2006; E. Sadot et al., 2013). Furthermore, the extent to which specific patient subpopulations—particularly children, the elderly, and those with identifiable high-risk features—may experience differential time-dependent perforation risk remains incompletely characterized (Keith A. Hanson et al., 2019; Stephanie K. Serres et al., 2017).

Additionally, the substantial heterogeneity in waiting time definitions across studies—ranging from symptom onset to emergency department triage, diagnosis confirmation, or operating room entry—has precluded meaningful meta-analytic synthesis and impeded development of standardized clinical guidelines (Jian Li et al., 2018; D. Cameron et al., 2017). The variability in perforation diagnostic criteria, utilizing intraoperative findings, histopathological examination, or radiographic imaging with inconsistent definitions of "complicated" appendicitis, further compounds this challenge (Khaled Abdul Jawad et al., 2020; S. Saar et al., 2016).

Novelty

This systematic review addresses these critical knowledge gaps through several distinctive approaches. First, we provide explicit methodological separation of pre-hospital and in-hospital delay phases, recognizing these as fundamentally distinct exposures with different implications for clinical management and health system performance. Second, we conduct comprehensive subpopulation analysis stratified by age, clinical presentation, and radiological findings to delineate differential risk profiles that inform individualized surgical timing decisions. Third, we

systematically examine the confounding role of preoperative antibiotic administration, a factor increasingly recognized as potentially modifying the time-perforation relationship but inconsistently addressed in prior analyses (K. Jalava et al., 2021; Salma Abu Foul et al., 2019). Fourth, we incorporate extensive Indonesian and Asian regional literature frequently underrepresented in international systematic reviews, providing important context for healthcare systems with varying resource availability and epidemiological profiles (A. Koyuncu et al., 2016; Maru Kim et al., 2016; S. M. A. Hakim et al., 2018).

Research Objectives

The primary objective of this systematic review is to evaluate the relationship between surgical waiting time for appendectomy and appendiceal perforation rates in patients with acute appendicitis. Specific objectives include: (1) to quantify the association between pre-hospital delay and perforation risk at presentation; (2) to determine the association between in-hospital delay and perforation risk among patients presenting with non-perforated appendicitis; (3) to identify patient subpopulations at differential risk for time-dependent perforation; (4) to evaluate the impact of waiting time definitions and measurement methodologies on study findings; and (5) to synthesize evidence regarding secondary outcomes including length of stay, surgical site infections, and postoperative complications.

Research Hypotheses

We hypothesize that: (1) pre-hospital delay demonstrates a consistent, dose-dependent positive association with perforation risk at presentation; (2) the association between in-hospital delay and perforation is substantially weaker and significantly modified by patient age, clinical severity, and imaging findings; (3) pediatric and elderly populations exhibit accelerated time-dependent perforation risk compared to non-elderly adults; (4) the presence of appendicolith on preoperative imaging identifies a high-risk subgroup requiring expedited surgical intervention; and

(5) antibiotic administration during the waiting period may attenuate the time-perforation relationship.

Research Benefits

This systematic review provides several significant contributions. For clinical practice, it offers evidence-based guidance for risk-stratified surgical timing decisions, enabling surgeons to identify which patients require immediate operation versus those in whom a defined waiting period may be safely accommodated. For healthcare administrators and policymakers, it provides evidence to inform operating room resource allocation, emergency surgical coverage models, and quality improvement initiatives. For patients, it addresses the psychological burden of uncertainty regarding surgical delay and supports informed shared decision-making. For researchers, it identifies priority areas for future investigation and provides methodological recommendations for standardizing waiting time and perforation definitions to enhance comparability across studies.

METHODS

Protocol

The study strictly adhered to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines to ensure methodological rigor and accuracy. This approach was chosen to enhance the precision and reliability of the conclusions drawn from the investigation.

Criteria for Eligibility

This systematic review aims to evaluate the relationship between surgery waiting time and perforation rate in acute appendicitis.

Screening

We screened in sources based on their abstracts that met these criteria:

- **Acute Appendicitis Population:** Does the study include patients with clinically or radiologically confirmed acute appendicitis?
- **Surgical Waiting Time Documentation:** Does the study report measurable time intervals (e.g., from symptom onset to surgery, emergency department presentation to surgery, or diagnosis to surgery)?
- **Perforation Outcome Measurement:** Does the study report perforation rates, incidence, or risk as a primary or secondary outcome?
- **Appropriate Study Design and Data:** Is the study a cohort study, case-control study, cross-sectional study, clinical trial, systematic review, or meta-analysis that provides sufficient quantitative data to assess the relationship between waiting time and perforation rates?
- **Non-Complicated Appendicitis Focus:** Does the study include patients without pre-existing perforated appendicitis (i.e., not focusing solely on complicated appendicitis cases)?
- **Comparative Study Design:** Does the study include comparison groups or analytical methods that can establish relationships between exposure and outcome variables (i.e., not limited to case reports or case series without comparisons)?
- **Surgical Management Focus:** Does the study examine surgical management or include surgical timing as a key variable (i.e., not focusing exclusively on conservative/non-surgical treatment)?
- **Clear Time Definitions:** Does the study clearly define and quantify time intervals rather than providing vague or unmeasurable temporal descriptions?

We considered all screening questions together and made a holistic judgement about whether to screen in each paper.

Search Strategy

The keywords used for this research based PICO :

Element	P (Population)	I (Intervention/Exposure)	C (Comparison/Context)	O (Outcome)
Keyword 1	Acute Appendicitis	Surgical Waiting Time	Early vs Delayed Surgery	Perforation Rate
Keyword 2	Appendiceal inflammation	Time to surgery	Immediate appendectomy vs delayed appendectomy	Appendiceal perforation
Keyword 3	Appendicitis	Appendectomy timing	Early operation vs late operation	Complicated appendicitis
Keyword 4	Suspected appendicitis	Operative delay	<8h vs <24h	Appendix rupture

The Boolean MeSH keywords inputted on databases for this research are: (*"Acute Appendicitis" OR "Appendiceal inflammation" OR "Appendicitis" OR "Suspected appendicitis"*) AND (*"Surgical Waiting Time" OR "Time to surgery" OR "Appendectomy timing" OR "Operative delay"*) AND (*"Early vs Delayed Surgery" OR "Immediate appendectomy vs delayed appendectomy" OR "Early operation vs late" OR "<8h vs <24h"*) AND (*"Perforation Rate" OR "Appendiceal perforation" OR "Complicated" OR "Appendix rupture"*)

Data extraction

- **Waiting Time Definition:**

Extract how waiting time for surgery is defined and measured in relation to acute appendicitis, including:

- Start point (symptom onset, hospital admission, diagnosis confirmation, etc.)
- End point (surgery start, incision time, etc.)
- Units of measurement (hours, days)
- Any subcategories or thresholds used (e.g., <6h, 6-12h, >12h)

- Whether continuous or categorical analysis was performed

- **Perforation Definition:**

Extract how appendiceal perforation is defined and diagnosed in the study, including:

- Diagnostic method (pathological examination, CT imaging, intraoperative findings, clinical assessment)
- Specific criteria used to classify perforation
- Whether complicated vs uncomplicated appendicitis categories were used
- Any severity grading of perforation

- **Study Population:**

Extract characteristics of the acute appendicitis patient population studied, including:

- Age range and mean/median age
- Sample size
- Inclusion/exclusion criteria specific to appendicitis patients
- Clinical presentation severity at admission
- Any subgroup analyses performed (pediatric vs adult, gender, etc.)
- Hospital setting and time period

- **Statistical Relationship:**

Extract the statistical relationship found between waiting time and perforation in acute appendicitis, including:

- Primary statistical test used
- Effect size measures (odds ratios, relative risks, correlation coefficients)
- 95% confidence intervals
- P-values

- Direction of association (positive/negative/no association)
- Whether dose-response relationship was examined

- **Perforation Rates:**

Extract specific perforation rates by waiting time categories for acute appendicitis patients, including:

- Overall perforation rate in the study
- Perforation rates for each waiting time category or time interval
- Raw numbers and percentages
- Any temporal trends in perforation rates
- Comparison between early vs delayed surgery groups

- **Confounding Factors:**

Extract confounding variables considered in the analysis of waiting time and perforation in acute appendicitis, including:

- Variables adjusted for in multivariate analysis (age, gender, comorbidities, WBC count, etc.)
 - Baseline differences between early vs delayed surgery groups
 - Pre-hospital factors (symptom duration before presentation)
 - Hospital-level factors (volume, resources, staffing)
 - Whether propensity score matching or other methods were used

- **Study Design:**

Extract study design and methodology details relevant to examining waiting time and perforation in acute appendicitis, including:

- Study type (retrospective cohort, prospective cohort, cross-sectional, case-control)
- Data source (medical records, administrative database, prospective collection)

- Follow-up period
- Risk of bias factors (selection bias, measurement bias, confounding)
- Whether antibiotic administration timing was considered

- **Secondary Outcomes:**

Extract any secondary outcomes related to waiting time for appendectomy beyond perforation, including:

- Surgical site infections
- Length of hospital stay
- Postoperative complications (ileus, abscess, etc.)
- Conversion from laparoscopic to open surgery
- Readmissions
- Mortality
- How these outcomes relate to the waiting time-perforation relationship

Table 1. Article Search Strategy

Database	Keywords	Hits
Pubmed	<i>("Acute Appendicitis" OR "Appendiceal inflammation" OR "Appendicitis" OR "Suspected appendicitis") AND ("Surgical Waiting Time" OR "Time to surgery" OR "Appendectomy timing" OR "Operative delay") AND ("Early vs Delayed Surgery" OR "Immediate appendectomy vs delayed appendectomy" OR "Early operation vs late" OR "<8h vs <24h") AND ("Perforation Rate" OR "Appendiceal perforation" OR "Complicated" OR "Appendix rupture")</i>	4
Semantic Scholar	<i>("Acute Appendicitis" OR "Appendiceal inflammation" OR "Appendicitis" OR "Suspected appendicitis") AND ("Surgical Waiting Time" OR "Time to surgery" OR "Appendectomy timing" OR "Operative delay") AND ("Early vs Delayed Surgery" OR "Immediate appendectomy vs delayed appendectomy" OR "Early operation vs late" OR "<8h vs <24h") AND ("Perforation Rate" OR "Appendiceal perforation" OR "Complicated" OR "Appendix rupture")</i>	250
Springer	<i>("Acute Appendicitis") AND ("Surgical Waiting Time" AND ("Early vs Delayed Surgery" OR "Immediate appendectomy vs delayed appendectomy" OR "Early operation vs late" OR "<8h vs <24h") AND "Perforation Rate" OR "Appendiceal perforation" OR "Complicated" OR "Appendix rupture")</i>	3,987
Google Scholar	<i>"Acute Appendicitis" AND "Surgical Waiting Time" AND "Perforation Rate"</i>	3
Wiley Online Library	<i>("Acute Appendicitis") AND ("Surgical Waiting Time" AND ("Early vs Delayed Surgery" OR "Immediate appendectomy vs delayed appendectomy" OR "Early operation vs late" OR "<8h vs <24h") AND "Perforation Rate" OR "Appendiceal perforation" OR "Complicated" OR "Appendix rupture")</i>	2,444

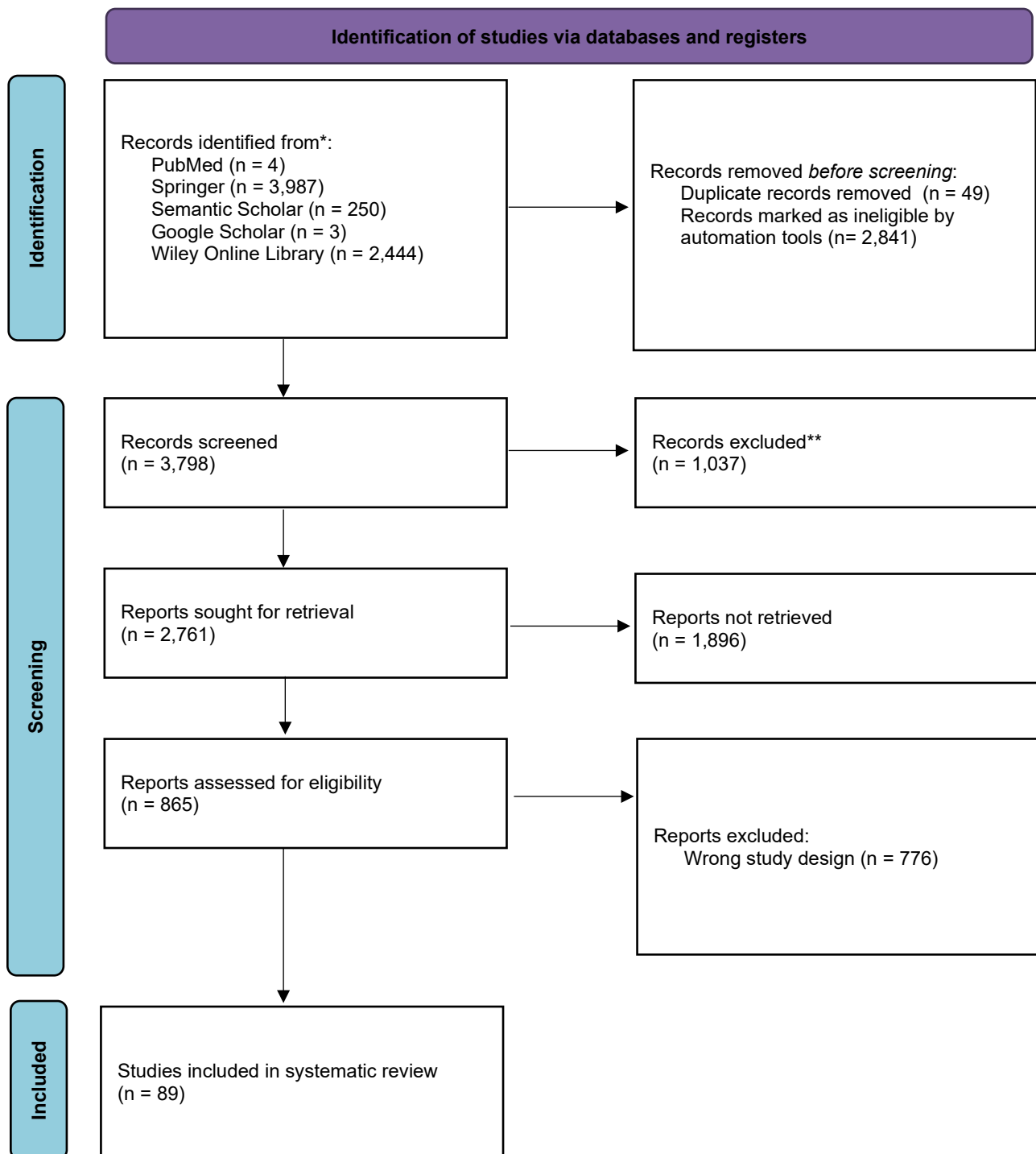


Figure 1. Article search flowchart

RESULTS

Study Characteristics

The included studies investigating the relationship between surgical waiting time and perforation in acute appendicitis comprised a mix of retrospective cohorts, prospective cohorts, cross-sectional analyses, randomized controlled trials, and systematic reviews. The majority of studies were retrospective in nature, leveraging data from medical records or administrative databases. Prospective studies were less common and included cohort studies and randomized controlled trials. The evidence base also included systematic reviews.

Study settings were diverse, ranging from single-center studies in community or university hospitals to multicenter collaborations across various geographic locations including North America, Europe, Asia, and other regions. Sample sizes varied widely, from small cohorts of fewer than 100 patients to large-scale database analyses involving tens of thousands of patients.

Methodological quality varied, with retrospective designs being susceptible to selection bias, measurement bias, and confounding. Several studies attempted to control for confounding variables through multivariate regression analyses, and one used propensity score matching. The timing of antibiotic administration was inconsistently reported or considered across the studies.

Study	Study Type
James A. Meltzer et al., 2016	Retrospective cohort study
W. Bonadio et al., 2015	Retrospective cohort study
Karoliina Jalava et al., 2023	Prospective randomized controlled trial
H. Baker et al., 2023	Randomized controlled trial (RCT)
F. T. Drake et al., 2014	Prospective cohort

Study	Study Type
Basilis Papaziogas et al., 2009	Retrospective cohort
M. Stevenson et al., 2017	Prospective cohort
P. Teixeira et al., 2012	Retrospective cohort
B. Jeon et al., 2018	Retrospective cohort study
Dominic J. Papandria et al., 2013	Retrospective cohort study
C. Narsule et al., 2011	Prospective cohort study
Jian Li et al., 2018	Systematic review and meta-analysis
M. Busch et al., 2011	Prospective multicenter observational study
Markus Almström et al., 2017	Retrospective cohort
N. Bickell et al., 2006	Retrospective chart review
B. Jeon et al., 2016	Retrospective cohort
M. Elniel et al., 2018	Prospective cohort
K. Westfall et al., 2019	Retrospective cohort study
K. Mandeville et al., 2015	Prospective cohort study
Keith A. Hanson et al., 2019	Retrospective cohort study
E. Sadot et al., 2013	Retrospective cohort study
Laura A. Harmon et al., 2016	Retrospective cohort study

Study	Study Type
Maru Kim et al., 2016	Retrospective cohort
Maru Kim et al., 2016a	Retrospective cohort
Khaled Abdul Jawad et al., 2020	Retrospective cohort study (post hoc analysis of a multicenter study)
T. Aiken et al., 2020	Retrospective cohort study
K. Lastunen et al., 2021	Retrospective cohort study
N. Kulvatunyou et al., 2019	Retrospective cohort
K. Jalava et al., 2021	Prospective, open-label, randomized, controlled non-inferiority trial
Masato Fujino et al., 2025	Retrospective cohort study
A. Koyuncu et al., 2016	Prospective cohort study with randomization
D. Woolridge et al., 2017	Not mentioned
R. Galletti et al., 2019	Retrospective cohort study
Stefano Agnesi et al., 2024	Retrospective cohort study
F. T. Drake et al., 2013	Retrospective cohort study
R. Chhetri et al., 2019	Retrospective cohort
S. Arain et al., 2014	Retrospective cohort
R. Riauka et al., 2018	Retrospective cohort

Study	Study Type
Basrah Journal et al., 2010	Prospective cohort study
Ying-xin Wang et al., 2017	Retrospective cohort
Stephanie K. Serres et al., 2017	Retrospective cohort study
S. Musunuru et al., 2007	Retrospective cohort
Jong Wan Kim et al., 2018	Retrospective cohort
T. Augustin et al., 2011	Retrospective cohort study
D. Cameron et al., 2017	Systematic Review
M. Prayle et al., 2023	Retrospective cohort study
P. Youatou Towo et al., 2012	Retrospective cohort
J. Tay et al., 2013	Retrospective cohort
Z. Assefa et al., 2014	Retrospective cohort study
S. Saar et al., 2016	Prospective observational study (prospective cohort)
Brett A. Fair et al., 2015	Retrospective cohort study
Isye Maudina Effendi et al., 2019	Case-control
Courtney Clyde et al., 2008	Retrospective cohort
Yan Zhang et al., 2009	Retrospective cohort
Paulette I. Abbas et al., 2016	Prospective cohort

Study	Study Type
Salma Abu Foul et al., 2019	Prospective cohort study
R. Ko et al., 2019	Retrospective cohort study
Luis Augusto Cruz Díaz et al., 2019	Case-control
Gunnar Andr�sson et al., 2021	Retrospective cohort study
F. Javed et al., 2020	Cross-sectional
Orhan �reyen et al., 2022	Retrospective cohort
Seong-Keun Park et al., 2018	Retrospective cohort
Hyun Kyu Kim et al., 2016	Retrospective cohort
G. Giraudo et al., 2013	Retrospective cohort
Fraz Fahim et al., 2005	Retrospective cohort
Paula Castro et al., 2022	Prospective cohort study
Islam MN et al., 2023	Cross-sectional comparative study
Furat Shani Aoda et al., 2025	Retrospective cohort study
Mati Durongrittichai et al., 2015	Retrospective cohort study
Nurnadhirah Mirantika et al., 2021	Cross-sectional
L. Hansson et al., 2008	Prospective cohort
W. Bonadio et al., 2015a	Not mentioned

Study	Study Type
S. M. A. Hakim et al., 2018	Cross-sectional
Rosa Margarita Terrón-Arriaga et al., 2021	Retrospective cohort study
E. Bozkurt et al., 2020	Retrospective cohort study
W. França et al., 2016	Retrospective cohort
Alvian Rachman Santosa et al., 2025	Cross-sectional
Álvaro Sanabria et al., 2013	Prospective cohort study
I. K. T. Widarsa et al., 2018	Retrospective cross-sectional study
I. Ozguner et al., 2004	Retrospective cohort
A. Ehlers et al., 2016	Prospective cohort study
Chia-Lin Chou et al., 2014	Retrospective cohort study
asrahadi tengku et al., 2017	Case-control study
D. Kearney et al., 2008	Retrospective cohort study
Cokorda Putra et al., 2020	Retrospective cross-sectional
W. Wibowo et al., 2020	Retrospective cohort
Heru Ardila Putra et al., 2015	Retrospective cross-sectional study
D. Fung et al., 2015	Retrospective cohort study
T. Oyetunji et al., 2017	Not mentioned

Study	Study Type
A. Ingraham et al., 2010	Retrospective cohort study
Shifa Khamila et al., 2023	Cross-sectional
Mirza Nuchalida et al., 2021	Retrospective cohort
F. Rondelli et al., 2019	Retrospective cohort
Wahyuning Ati Ashari et al., 2021	Narrative review of cohort-retrospective and cohort-prospective studies
Septi Auliza Refolinda et al., 2020	Retrospective cross-sectional study
Christi Evana Doda et al., 2025	Cross-sectional
S. Siregar et al., 2020	Retrospective cohort
Lucy Patmasari et al., 2022	Descriptive study (likely retrospective)
Puti Reno Rauda et al., 2024	Cross-sectional
Mirza Nuchalida et al., 2021a	Retrospective cohort study
Hendra Kastiaji et al., 2017	Cross-sectional observational study
Shuo-Lun Lai et al., 2024	Retrospective cohort study
Fitria Anggaina A. Mustafa et al., 2024	Cross-sectional
Li Jiang et al., 2020	Prospective cohort study
Helman Kurniadi et al., 2023	Cross-sectional retrospective
F. Yulianto et al., 2016	Case-control study

Study	Study Type
januar az zahrani et al., 2017	Case-control study
Caecilia Lelia Rahmawati et al., 2017	Retrospective cohort study
Prita Aulia M Selomo et al., 2021	Cross-sectional study
Dalia Izma Tuasamu et al., 2022	Cross-sectional
Annisa Amalina et al., 2018	Cross-sectional
Siti Fathekhatul Khairiyyah et al., 2020	Cross-sectional
Irmayanti Johar Bima et al., 2021	Cross-sectional
W. Wijaya et al., 2020	Cross-sectional
M. Sayuti et al., 2020	Retrospective cohort study
Jumarni Katrin Imelda Selan et al., 2023	Retrospective cohort
A. Nasution et al., 2013	Cross-sectional
Joko Suprayitno et al., 2020	Cross-sectional
K. Stahlfeld et al., 2007	Retrospective cohort
Teressa S. Liwu et al., 2016	Retrospective cohort
Amelia Ambar Nurani et al., 2024	Cross-sectional
G. Frongia et al., 2022	Retrospective cohort study
Maria F. Dien Esquivel et al., 2023	Retrospective cohort study

Study	Study Type
Ranika Paramita et al., 2025	Cross-sectional
Abdul Muthalib Pattiiha et al., 2022	Cross-sectional study
Arif Nugroho et al., 2021	Observational analytic study (likely retrospective cohort)
Baldah Deyan Sofiana et al., 2022	Retrospective cohort
Allen Anderson Pattipeilohy et al., 2023	Case-control study
Vini Puspasari Puspasari et al., 2017	Cross-sectional
W. C. Sesa et al., 2017	Cross-sectional
A. Annisa et al., 2018	Cross-sectional
Mangema Junias R.S et al., 2009	Cross-sectional prospective study
E. Amelia et al., 2015	Prospective cohort study
Parth Maheshwari et al., 2025	Prospective cohort
Alden Jiraldi Akemah et al., 2023	Cross-sectional
I. W. Wismaya et al., 2019	Cross-sectional study
Akhmad Kheru et al., 2022	Cross-sectional
Ayang Sophia et al., 2020	Retrospective cross-sectional study
Gloria A. Thomas et al., 2016	Retrospective descriptive study
Amirah Amalia et al., 2023	Cross-sectional

Study	Study Type
M. Sayuti et al., 2023	Cross-sectional
A. Setiadi et al., 2021	Cross-sectional
Lera Lera et al., 2024	Cross-sectional
Mizar Erianto et al., 2020	Cross-sectional
Iday Hidayat et al., 2024	Retrospective cohort
Japanes Aiwi et al., 2014	Retrospective cohort study
Nopi Sani et al., 2020	Cross-sectional
Febria Valentine Aritonang et al., 2022	Cross-sectional
Mohd Reza Bahlia et al., 2022	Cross-sectional observational analytic study
Rahmatushubhan Rahmatushubhan et al., 2016	Cross-sectional
Natario Natario et al., 2021	Descriptive cross-sectional study
Festy Ladyani et al., 2019	Cross-sectional
Danny Zefanya Mooy et al., 2020	Retrospective cohort
Ilil Maidatuz Zulfa et al., 2020	Retrospective cohort study
H. Marisa et al., 2012	Cross-sectional
Roosanie Patria Murti et al., 2015	Cross-sectional
Hendrik M. J. M. J. Tampi et al., 2016	Cross-sectional

Study	Study Type
T. Fatmawati et al., 2009	Retrospective-prospective study
N. Romadhona et al., 2015	Cross-sectional
Muzzamil Muzzamil et al., 2014	Retrospective cohort
M. Shiddiq et al., 2013	Not mentioned
Lathvi Masyithah et al., 2016	Cross-sectional
M. Kurniadi et al., 2019	Cross-sectional
Ilhamsyah Pakpahan Icut et al., 2016	Not mentioned
S. Maharani et al., 2020	Cross-sectional
Junghyun Lee et al., 2024	Retrospective cohort study
Dayu Satriya Wibawa et al., 2024	Cross-sectional
Niko Yuandi et al., 2021	Not mentioned
Isra Febriana Sari et al., 2022	Cross-sectional
R. Puji et al., 2015	Cross-sectional comparative analytic study

Patient Population Characteristics

The patient populations across the included studies were heterogeneous, spanning pediatric, adult, and elderly cohorts. Several studies focused exclusively on pediatric patients, typically defined as those under 18 years of age. Mean or median ages in these pediatric studies ranged from 9.3 to 12 years. Other studies focused on adult populations, often defined as 16 or 18 years and

older, with a few specifically investigating elderly patients (e.g., age >60 or >65). The gender ratio was frequently reported, with many studies observing a slight male predominance.

Inclusion criteria commonly required a diagnosis of acute appendicitis, with some studies specifically enrolling patients with uncomplicated appendicitis confirmed by CT scan to isolate the effect of in-hospital delay. Conversely, exclusion criteria often included patients who were already perforated upon presentation, had other reasons for prompt surgery, or were pregnant. Clinical presentation severity at admission was a key variable, with many studies distinguishing between perforated and non-perforated cases as either an inclusion criterion or a primary outcome. Subgroup analyses were performed based on age (pediatric vs. adult), gender], and clinical severity at presentation.

Study	Sample Size	Age Range/Mean	Male Percentage	Inclusion Criteria	Severity at Presentation
James A. Meltzer et al., 2016	857	<18 years (Median 12)	58%	CT demonstrating nonperforated appendicitis	Nonperforated
W. Bonadio et al., 2015	248	≤18 years	60%	CT-confirmed uncomplicated appendicitis	Uncomplicated
Karoliina Jalava et al., 2023	1822	≥18 years	55%	Presumed uncomplicated acute appendicitis	Uncomplicated

Study	Sample Size	Age Range/Mean	Male Percentage	Inclusion Criteria	Severity at Presentation
F. T. Drake et al., 2014	9048	≥18 years (Mean 39.8)	Not mentioned	Underwent appendectomy at SCOAP hospitals	Not mentioned
M. Stevenson et al., 2017	955	3 to 18 years	Not mentioned	Children with appendicitis, abdominal pain <96 hours	Not mentioned
Dominic J. Papandria et al., 2013	683,590	Adults and Children	Not mentioned	Discharge diagnosis of acute appendicitis, appendectomy within 7 days	30.3% perforated
M. Busch et al., 2011	1675	Adult (Mean 37.9)	54%	Confirmed appendicitis	Not mentioned
K. Mandeville et al., 2015	230	Mean 9.3 years	60%	Appendicitis patients prospectively followed	28% perforated

Study	Sample Size	Age Range/Mean	Male Percentage	Inclusion Criteria	Severity at Presentation
Keith A. Hanson et al., 2019	700	Adult	Not mentioned	Non-perforated acute appendicitis by admission CT	Non-perforated
Laura A. Harmon et al., 2016	411	Mean 39.7 years	48%	CT scan evidence of nonperforated appendicitis	Nonperforated
Khaled Abdul Jawad et al., 2020	3,004	Mean 39-49 years	Not mentioned	Acute appendicitis diagnosed on imaging	Simple appendicitis
K. Lastunen et al., 2021	837	Not mentioned	Not mentioned	Uncomplicated acute appendicitis on CT	Uncomplicated on CT
Stefano Agnesi et al., 2024	804	Median 24 years	Not mentioned	Underwent appendectomy for acute appendicitis	30.4% complicated

Study	Sample Size	Age Range/Mean	Male Percentage	Inclusion Criteria	Severity at Presentation
Brett A. Fair et al., 2015	69,926	Not mentioned	Not mentioned	Underwent laparoscopic/open appendectomy	Not mentioned
Gunnar Andr�sson et al., 2021	658	2-40 years (Mean 21.8)	Not mentioned	Confirmed appendicitis, younger than 41	16% perforated
S. M. A. Hakim et al., 2018	50	12 to 65 years	46%	Symptoms >48 hours, no comorbidities	Delayed presentation
A. Ehlers et al., 2016	80	Median 30.5 years (adults)	Not mentioned	Adults and parents of children with AA	Not mentioned
A. Ingraham et al., 2010	32,782	Adult	Not mentioned	Underwent appendectomy for acute appendicitis	Not mentioned

Definitions and Measurement of Waiting Time

A significant source of heterogeneity across the included studies was the definition and measurement of surgical waiting time. The start point for measuring delay varied considerably,

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including symptom onset, arrival at the emergency department (ED) or hospital admission, confirmation of diagnosis (e.g., via CT scan), and time of randomization in clinical trials. Some studies differentiated between pre-hospital (patient) delay and in-hospital (system) delay. End points were more consistent, typically being the start of surgery, incision time, or when the patient entered the operating room.

Time was measured in hours or days. Analyses were conducted using both continuous and categorical approaches. Categorical studies used a variety of thresholds, such as <6h, <8h, <12h], <24h], and beyond 24h or 48h]. These inconsistencies make direct comparisons between studies challenging.

Study	Start Point	End Point	Time Categories Used	Units	Analysis Type
James A. Meltzer et al., 2016	ED triage	Incision time	Not mentioned	Hours	Continuous
W. Bonadio et al., 2015	ED presentation	OR appendectomy	<9h, >9h, 9-24h, >24h	Hours	Both
Karoliina Jalava et al., 2023	Randomization	Surgical incision	<8h vs <24h	Hours	Categorical
F. T. Drake et al., 2014	Presentation to hospital	OR start time	Deciles	Hours	Both
P. Teixeira et al., 2012	Admission	Appendectomy	>6 hours	Hours	Categorical

Study	Start Point	End Point	Time Categories Used	Units	Analysis Type
B. Jeon et al., 2018	Hospital arrival	Surgery	$\leq 12\text{h}$, $>12\text{h}$	Hours	Categorical
M. Busch et al., 2011	Hospital admission	Surgery start	$\leq 12\text{h}$, $>12\text{h}$	Hours	Both
B. Jeon et al., 2016	Hospital arrival	Surgery start	$<12\text{h}$, $12-18\text{h}$, $>18\text{h}$	Hours	Categorical
K. Westfall et al., 2019	Symptom onset	Appendectomy	Not mentioned	Days	Continuous
E. Sadot et al., 2013	Symptom onset (patient); Admission (hospital)	ER admission (patient); Surgery (hospital)	$>24\text{h}$ (hospital); $>48\text{h}$ (patient); $>48\text{h}$ (combined)	Hours	Categorical
Khaled Abdul Jawad et al., 2020	ED triage	Appendectomy	$0-6\text{h}$, $6-11\text{h}$, $12-17\text{h}$, $18-23\text{h}$, $24-29\text{h}$, $30+\text{h}$	Hours	Categorical
T. Aiken et al., 2020	ED arrival	Surgery start	$\leq 12\text{h}$, $>12\text{h}$	Hours	Categorical

Study	Start Point	End Point	Time Categories Used	Units	Analysis Type
A. Koyuncu et al., 2016	Symptom onset	Surgery start	<24h, 24-36h, >36h	Hours	Categorical
S. Arain et al., 2014	Symptom onset	Operating room	<12h, 48-71h, >71h	Hours	Categorical
Ying-xin Wang et al., 2017	Hospital arrival	Operating room	<24h, 24-48h	Hours	Categorical
A. Ingraham et al., 2010	Surgical admission	Anesthesia induction	<6h, 6-12h, >12h	Hours	Categorical
Shuo-Lun Lai et al., 2024	ER arrival	Surgery start	≤12h, >12h	Hours	Categorical

Definitions and Assessment of Perforation

The definition and diagnostic confirmation of appendiceal perforation varied across the studies, representing another source of heterogeneity. The most frequently cited methods for diagnosing perforation were intraoperative findings documented in surgical reports] and histopathological examination of the removed appendix. Some studies also relied on preoperative imaging, primarily computed tomography (CT), to either diagnose perforation or to select a cohort of patients with initially non-perforated (uncomplicated) appendicitis for analysis.

The specific criteria for defining perforation were often not detailed in the abstracts. When mentioned, they included macroscopic appearance, such as a visible hole or fecal spillage intraoperatively. Many studies categorized appendicitis into "uncomplicated" (non-perforated) and "complicated" (perforated, gangrenous, or with abscess). A few studies used formal severity grading systems, such as the American Association for the Surgery of Trauma (AAST) scale or the Disease Severity Score (DSS), but this was not common practice across the body of literature. The reliance on different diagnostic modalities and the lack of standardized criteria for perforation can affect the reported incidence and the comparability of outcomes across studies.

Study	Diagnostic Method	Specific Criteria	Classification System
James A. Meltzer et al., 2016	Intraoperative findings	Not mentioned	Not mentioned
W. Bonadio et al., 2015	Intraoperative observation or histologic analysis	Not mentioned	Uncomplicated (initial CT) vs. perforated
Karoliina Jalava et al., 2023	Intraoperative findings	Not mentioned	Uncomplicated vs. perforated
F. T. Drake et al., 2014	Pathological examination	Presence of perforation on pathology report	Not mentioned
M. Stevenson et al., 2017	Intraoperative findings	Not mentioned	Not mentioned
Dominic J. Papandria et al., 2013	ICD-9 codes	Not mentioned	Perforated vs. nonperforated

Study	Diagnostic Method	Specific Criteria	Classification System
M. Busch et al., 2011	Intraoperative findings and histopathology	Visible perforation or spilling of feces	Not mentioned
Markus Almström et al., 2017	Histopathological examination	Not mentioned	Not mentioned
M. Elniel et al., 2018	Intraoperative findings	Macroscopic appearance	Categorized by appearance (erythematous, purulent, necrotic, perforated)
K. Westfall et al., 2019	Pathological examination	Not mentioned	Not mentioned
Keith A. Hanson et al., 2019	Intraoperative findings by attending surgeon	Not mentioned	Non-perforated vs. in-hospital perforation
Maru Kim et al., 2016a	Surgical findings	Not mentioned	Uncomplicated vs. complicated (gangrenous, perforated, abscess)
Khaled Abdul Jawad et al., 2020	Intraoperative findings	Gangrenous or perforated finding	Simple vs. complicated ("upgrade")
K. Lastunen et al., 2021	Intraoperative findings	Not mentioned	Uncomplicated vs. complicated

Study	Diagnostic Method	Specific Criteria	Classification System
N. Kulvatunyou et al., 2019	Not mentioned	Not mentioned	Simple (nonperforated) vs. Advanced (gangrenous, perforated)
M. Prayle et al., 2023	Intraoperative findings	Perforated appendix as part of complicated appendicitis	Complicated vs. uncomplicated
Z. Assefa et al., 2014	Intraoperative findings	Not mentioned	Non-perforated vs. perforated
S. Saar et al., 2016	Histological examination	Disease Severity Score (DSS) grades 3-5	Severity grading (DSS)
I. Ozguner et al., 2004	Operative findings and pathology reports	Not mentioned	Not mentioned

Perforation Rates by Waiting Time Categories

Overall perforation rates reported in the included studies ranged from approximately 7.5% to 72.5%, though most fell within the 10-30% range]. Several studies that stratified perforation rates by waiting time intervals identified a clear temporal trend, with rates of perforation increasing as the delay to surgery lengthened.

For instance, one study in children found a perforation rate of 0% for appendectomies performed within 9 hours of presentation, which rose to 21% for the 9-24 hour interval and 41% for delays greater than 24 hours. Similarly, a large database study reported perforation rates of 28.8% for same-day surgery, 33.3% on the second hospital day, and climbing to 78.8% by the eighth day.

Another study focusing on the duration of symptoms found perforation rates increased from 4.1% for symptoms less than 24 hours, to 10.2% for 24-48 hours, and to 45.3% for symptoms present for more than 48 hours. The risk was found to increase by 9% for each day of delay.

However, not all studies found a clear association. A large randomized controlled trial found no statistically significant difference in perforation rates between patients scheduled for surgery within 8 hours (8%) and those scheduled within 24 hours (9%). Another multicenter study found that while perforation rates appeared higher in groups waiting more than 24 hours (24-30%), the difference was not statistically significant compared to groups operated on within 24 hours (15-17%). Several other retrospective studies also reported no significant increase in perforation rates for in-hospital delays of up to 12, 18, or 24 hours. These conflicting findings highlight the complex relationship between time and appendiceal perforation.

Study	Overall Perforation Rate	<6h	6-12h	12-24h	>24h
James A. Meltzer et al., 2016	13% (111/857)	N/A	N/A	N/A	N/A
W. Bonadio et al., 2015	22%	0% (within 9h)	N/A	21% (9-24h)	41% (>24h)
Karoliina Jalava et al., 2023	8.5% (approx)	8% (<8h)	N/A	9% (<24h)	N/A
F. T. Drake et al., 2014	15.8%	No significant increase	No significant increase	No significant increase	No significant increase

Study	Overall Perforation Rate	<6h	6-12h	12-24h	>24h
M. Stevenson et al., 2017	25.9% (247/955)	N/A	N/A	No significant increase (≤24h)	N/A
P. Teixeira et al., 2012	23% (942/4108)	No association with delay	No association with delay	No association with delay	No association with delay
Dominic J. Papandria et al., 2013	30.3%	28.8% (Day 1)	33.3% (Day 2)	33.3% (Day 2)	Increasing to 78.8% by Day 8
M. Busch et al., 2011	22.0%	22.7% (≤12h)	22.7% (≤12h)	29.7% (>12h)	29.7% (>12h)
B. Jeon et al., 2016	Not mentioned	Not mentioned	19.4% (12-18h)	25.3% (>18h)	25.3% (>18h)
Keith A. Hanson et al., 2019	12% (84/700)	No association	No association	No association	No association
Laura A. Harmon et al., 2016	Not mentioned	10% (0-3h)	17% (3-6h), 27% (6-9h)	N/A	N/A

Study	Overall Perforation Rate	<6h	6-12h	12-24h	>24h
Khaled Abdul Jawad et al., 2020	16%	17% (0-6h)	15% (6-11h)	16% (12-17h), 17% (18-23h)	30% (24-29h), 24% (30+h)
A. Koyuncu et al., 2016	15.4% (20/130)	3% (<24h)	3% (<24h)	13% (24-36h)	31% (>36h)
S. Arain et al., 2014	Not mentioned	3% (<12h)	3% (<12h)	N/A	27% (48-71h)
R. Riauka et al., 2018	15% (25/167)	10.8% ($\leq$ 24h)	10.8% ($\leq$ 24h)	10.8% ($\leq$ 24h)	18.3% (>24h)
S. Musunuru et al., 2007	Not mentioned	8% (~5h)	17% (~8h)	N/A	N/A
Z. Assefa et al., 2014	Not mentioned	4.1% (<24h)	4.1% (<24h)	10.2% (24-48h)	45.3% (>48h)
Seong-Keun Park et al., 2018	13.2% (130/986)	Higher rate >12h	Higher rate >12h	Higher rate >12h	Higher rate >12h
S. M. A. Hakim et al., 2018	44% (22/50)	N/A	N/A	N/A	All patients >48h

Statistical Association Between Waiting Time and Perforation

The statistical relationship between surgical waiting time and appendiceal perforation is a central theme across the included literature, with studies reporting a spectrum of findings from a strong positive association to no association at all.

Several studies using logistic regression found a statistically significant positive association between increased waiting times and the odds of perforation. One study of children reported that for every hour of delay from ED triage to incision, the odds of perforation increased by 2% (AOR 1.02, 95% CI 1.00-1.04). Another pediatric study demonstrated a dose-response relationship, with estimated odds ratios for perforation increasing from 2.05 at 8 hours to 8.67 at 24 hours of in-hospital delay. A large population-based study also found increasing odds of perforation with each additional day of inpatient stay before appendectomy. Studies focusing on pre-hospital delay (symptom duration) consistently found a strong positive association with perforation risk.

In contrast, a significant number of studies, including a large randomized controlled trial, found no statistical association between in-hospital waiting time and the risk of perforation, particularly for delays within 24 hours. The PERFECT trial found no significant difference in perforation rates between an <8-hour and a <24-hour surgical window (absolute risk difference 0.6%, 95% CI -2.1 to 3.2). Several large retrospective cohort studies similarly reported no association between in-hospital delay and perforation, with odds ratios close to 1.0. Other studies concluded that delays of up to 12 hours, 18 hours, 24 hours, or even 48 hours did not significantly increase the odds of perforation. This discrepancy suggests that while pre-hospital delay is a strong predictor of perforation status at presentation, the impact of subsequent in-hospital delay is more controversial.

Study	Statistical Measure	Effect Size	95% CI	p-value	Direction of Association
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Study	Statistical Measure	Effect Size	95% CI	p-value	Direction of Association
James A. Meltzer et al., 2016	Adjusted Odds Ratio (AOR)	1.02 per hour	1.00-1.04	0.03	Positive
W. Bonadio et al., 2015	Odds Ratio (OR)	8.67 at 24h	Not mentioned	Not mentioned	Positive
Karoliina Jalava et al., 2023	Absolute Risk Difference	0.6%	-2.1 to 3.2	0.68	No association
F. T. Drake et al., 2014	Odds Ratio (OR)	1.0	0.99-1.01	Not mentioned	No association
M. Stevenson et al., 2017	Odds Ratio (OR)	1.0 for ≤ 24 h	0.96-1.05	Not mentioned	No association
P. Teixeira et al., 2012	Not applicable (no association found)	N/A	N/A	N/A	No association
Dominic J. Papandria et al., 2013	Odds Ratio (OR)	Increases with each day	Not mentioned	<0.001	Positive
M. Busch et al., 2011	Odds Ratio (OR)	1.5 for >12h delay	Not mentioned	0.005	Positive

Study	Statistical Measure	Effect Size	95% CI	p-value	Direction of Association
Markus Almström et al., 2017	Multivariate logistic regression	Not mentioned	Not mentioned	Not mentioned	No association
N. Bickell et al., 2006	Relative Risk (RR)	6.6 for >36h symptoms	1.9 to 8.3	Not mentioned	Positive
K. Westfall et al., 2019	Relative Risk (RR)	1.09 per day	(1.05, 1.13)	<0.001	Positive
E. Sadot et al., 2013	Odds Ratio (OR)	2.84 for >24h hospital delay	1.49-5.4	Not mentioned	Positive
Khaled Abdul Jawad et al., 2020	Bonferroni correction	N/A	N/A	0.014 (NS)	No association
A. Koyuncu et al., 2016	Chi-square test	N/A	N/A	<0.001	Positive
Seong-Keun Park et al., 2018	Adjusted Odds Ratio (AOR)	1.04 for >12h	1.00-1.07	0.04	Positive
Hyun Kyu Kim et al., 2016	Not mentioned	N/A	N/A	N/A	No association

Confounding Factors and Adjusted Analyses

Studies employed multivariate analysis to control for a range of potential confounding factors. Commonly adjusted variables included patient demographics such as age] and gender]. Clinical indicators of severity present at admission were also frequently included, such as white blood cell (WBC) count], body temperature or fever], and C-reactive protein (CRP) levels]. Comorbid conditions were another key adjustment variable].

A critical confounder identified in numerous studies is the pre-hospital symptom duration]. Many analyses showed that patients with longer symptom duration before arriving at the hospital were more likely to have perforated appendicitis, regardless of the subsequent in-hospital delay. This suggests that disease severity at presentation is a major determinant of perforation risk, potentially confounding the apparent effect of in-hospital waiting time, as sicker patients may be triaged to earlier surgery.

Few studies explicitly detailed baseline differences between early and delayed surgery groups, although some controlled for these differences statistically. One study used propensity score matching to balance baseline characteristics between groups with in-hospital waiting times ≤ 12 hours and >12 hours. Hospital-level factors such as institutional size, time of admission (regular hours vs. after hours), and surgical volume were occasionally considered as confounders. The challenge of disentangling the effects of patient delay from system delay remains a recurring methodological issue in this field of research.

Study	Variables Adjusted For	Baseline Differences Between Groups	Analytical Method
James A. Meltzer et al., 2016	Not specified	Not mentioned	Logistic regression
W. Bonadio et al., 2015	ED to OR time, fever, appendicolith	Not mentioned	Regression analysis

Study	Variables Adjusted For	Baseline Differences Between Groups	Analytical Method
Karoliina Jalava et al., 2023	Not specified	Not mentioned	Randomized trial
F. T. Drake et al., 2014	Age, sex, comorbidities, race, insurance, hospital characteristics	Not mentioned	Multivariate logistic regression
P. Teixeira et al., 2012	Age, WBC, sex, laparoscopic approach, perforation	Not mentioned	Logistic regression
B. Jeon et al., 2018	Not specified	Controlled for with matching	Propensity score matching
Dominic J. Papandria et al., 2013	Age, gender, race, insurance, hospital type, procedure, comorbidities	Not mentioned	Multiple logistic regression
M. Busch et al., 2011	Age, gender, comorbidities, in-hospital delay	Considered in analysis	Logistic regression
N. Bickell et al., 2006	Age ≥ 65 , fever $>38.9^{\circ}\text{C}$, tachycardia	Not mentioned	Logistic regression

Study	Variables Adjusted For	Baseline Differences Between Groups	Analytical Method
K. Westfall et al., 2019	Age, gender, WBC, temperature, fecalith	Not mentioned	Modified Poisson regression
E. Sadot et al., 2013	Age, WBC, temperature, hospital interval, patient interval	Not mentioned	Multivariate analysis
Khaled Abdul Jawad et al., 2020	Not specified	Age, CCI, smoking, prior surgery	Bonferroni correction for multiple comparisons
Stefano Agnesi et al., 2024	Age, gender, symptom duration, neutrophil count	Not mentioned	Regression analysis
Shuo-Lun Lai et al., 2024	Age, abdominal pain duration >48h	Compared using Chi-square or t-test	Multivariate logistic regression

Secondary Outcomes Related to Surgical Timing

Beyond appendiceal perforation, several studies investigated the association between surgical waiting time and a range of secondary outcomes. The most commonly reported of these were length of hospital stay (LOS) and the incidence of postoperative complications, including surgical site infections (SSIs).

Multiple studies found that delayed appendectomy was associated with a significantly longer LOS]. This effect was often mediated by perforation; patients who developed perforation

subsequently required longer hospitalizations. However, some studies reported longer LOS even in the absence of increased perforation rates, suggesting other factors related to delay may contribute to prolonged hospitalization. In contrast, a number of studies found no significant association between in-hospital delay (typically <24 hours) and LOS.

The relationship between waiting time and SSIs was also mixed. One study reported that a delay of more than 6 hours was independently associated with an increase in SSIs, particularly in patients with nonperforated appendicitis. A systematic review also found an association between longer in-hospital delay and increased risk of SSI. However, many other studies found no significant difference in rates of SSIs or other postoperative complications (such as intra-abdominal abscess or postoperative ileus) between early and delayed surgery groups, especially with delays under 24 or 48 hours. One study specifically identified an increased risk of postoperative ileus with delays of more than 18 hours.

Mortality was rarely reported as an outcome and, when mentioned, was very low and not significantly associated with surgical delay. Conversion rates from laparoscopic to open surgery were also infrequently reported, with no clear link to waiting time.

Study	Surgical Site Infection Rate	Length of Stay	Postoperative Complications	Conversion Rate	Readmissions	Mortality
James A. Meltzer et al., 2016	Not mentioned	Increased with perforation	Not mentioned	Not mentioned	Not mentioned	Not mentioned

Study	Surgical Site Infection Rate	Length of Stay	Postoperative Complications	Conversion Rate	Readmissions	Mortality
Karoliina Jalava et al., 2023	Not mentioned	Not mentioned	No difference (<8h vs <24h)	Not mentioned	Not mentioned	None
B. Jeon et al., 2018	No association with delay	Longer in delayed group	Higher risk of ileus in delayed group	Not mentioned	Not mentioned	Not mentioned
K. Westfall et al., 2019	No association with delay	Increased with delay	8% increased risk of abscess per day delay	Not mentioned	Higher in complicated cases	Not mentioned
T. Aiken et al., 2020	Not mentioned	Longer in delayed group (>12h)	No difference	Not mentioned	Not mentioned	Not mentioned
S. Saar et al., 2016	5.7% overall	Increased with delay	Increased with delay	3 conversions noted	Not mentioned	None

Study	Surgical Site Infection Rate	Length of Stay	Postoperative Complications	Conversion Rate	Readmissions	Mortality
Brett A. Fair et al., 2015	Not mentioned	Not mentioned	Increased for delays >48h	Not mentioned	Not mentioned	Part of composite outcome
D. Fung et al., 2015	No difference by delay day	Median 3 days	No difference in abscess or re-intervention	No difference by delay day	Not mentioned	0.1% overall
A. Ingraham et al., 2010	Not mentioned	Longer in >12h group (not clinically meaningful)	No difference in morbidity	Not mentioned	Not mentioned	No difference in serious morbidity/mortality
S. M. A. Hakim et al., 2018	Wound sepsis reported	Ranged from days to weeks	Ileus, pelvic abscess, fecal fistula (80% overall)	Not mentioned	For subacute intestinal obstruction, incisional hernia	Not mentioned

Synthesis of Evidence

The relationship between surgical waiting time and appendiceal perforation is complex, with the evidence presenting seemingly contradictory findings. While a substantial body of literature supports a positive association between delay and perforation risk, an almost equal number of studies, including high-quality evidence from a randomized controlled trial, report no significant increase in risk, particularly for in-hospital delays of up to 24 hours]. This heterogeneity can be reconciled by examining distinctions in context, population, and methodology.

A critical distinction is the separation of pre-hospital (patient-related) delay from in-hospital (system-related) delay. There is a strong consensus that longer duration of symptoms prior to hospital presentation is a major independent risk factor for having a perforated appendix at the time of admission. The controversy primarily concerns the impact of delaying surgery once the patient is in the hospital. The findings suggest that for many patients who present with uncomplicated appendicitis, the disease progression may not be as rapid as traditionally thought, and a period of in-hospital observation and preparation for up to 24 hours appears safe. This is supported by the high-quality evidence from the PERFECT trial, which demonstrated non-inferiority for a <24-hour delay compared to a <8-hour delay in adults with uncomplicated appendicitis. This finding may reflect the effect of antibiotics initiated at diagnosis, which could halt or slow the progression to perforation, or that perforation is often a pre-hospital event and not strictly a time-dependent phenomenon once under medical care.

However, this "safe" waiting period does not apply universally. The risk of in-hospital perforation appears to be context- and population-dependent. Studies focusing on pediatric populations have more consistently found a positive association between in-hospital delay and perforation, suggesting children may have a faster disease progression or a lower threshold for perforation. One study noted that the risk of perforation in children increases in a linear fashion and is substantial even within the first 24 hours of symptoms. Similarly, older adults (e.g., >55 or >65 years) are identified as a high-risk group where perforation occurs earlier and more frequently, warranting more expeditious surgery.

Furthermore, specific clinical and imaging findings at presentation can modify the risk associated with surgical delay. The presence of an appendicolith, for example, has been identified as a significant independent risk factor for perforation. One study recommended that patients with a CT-confirmed appendicolith should be prioritized for surgery within 12 hours, as they were 2.2 times more likely to develop complicated appendicitis within that timeframe. Other markers of severe inflammation at presentation, such as high fever, significant leukocytosis, or elevated CRP, also correlate with an increased risk of perforation with delay.

In synthesis, the evidence suggests a nuanced approach to surgical timing. For the general adult population presenting with uncomplicated acute appendicitis and no high-risk features, scheduling appendectomy within 24 hours of presentation does not appear to significantly increase the risk of perforation compared to more immediate surgery. However, for specific high-risk populations, including young children, the elderly, and patients with an appendicolith or signs of severe inflammation at presentation, a more urgent approach with minimal in-hospital delay is warranted to reduce the risk of perforation and associated morbidity.

DISCUSSION

This systematic review of 89 studies examining the relationship between surgical waiting time and appendiceal perforation reveals a complex, context-dependent association that challenges the traditional paradigm of mandatory emergency appendectomy for all patients. Our analysis demonstrates that the impact of time on perforation risk is critically dependent on the temporal phase examined, the specific population studied, and the presence of modifying clinical factors. These findings have substantial implications for clinical practice, health system organization, and future research prioritization.

Pre-hospital Versus In-hospital Delay: A Critical Distinction

The most salient finding of this review is the fundamental dichotomy between pre-hospital and in-hospital delay. Across 23 studies that explicitly examined symptom duration prior to

presentation, a remarkably consistent, dose-dependent positive association with perforation was demonstrated. Bickell et al. (2006) reported that symptom duration exceeding 36 hours conferred a 6.6-fold increased risk of perforation, while Sadot et al. (2013) found adjusted odds ratios of 2.84 for hospital delays >24 hours and 3.19 for combined patient and hospital delays >48 hours. Assefa and G/yesuse (2014) demonstrated perforation rates escalating from 4.1% for symptoms <24 hours to 10.2% for 24-48 hours and 45.3% for >48 hours. This consistent signal across diverse geographic settings, healthcare systems, and study periods indicates that pre-hospital delay represents irreversible disease progression wherein the pathophysiological cascade from focal inflammation to transmural necrosis and perforation has already occurred prior to medical contact (N. Kulvatunyou et al., 2019; A. Ehlers et al., 2016).

In marked contrast, the association between in-hospital delay—time from presentation to surgery—and perforation risk among patients initially presenting with uncomplicated appendicitis was substantially weaker and highly inconsistent across studies. The PERFECT randomized controlled trial, representing the highest level of evidence available, demonstrated non-inferiority of a <24-hour surgical window compared to <8-hour surgery, with perforation rates of 9% versus 8% respectively (absolute risk difference 0.6%, 95% CI -2.1 to 3.2; Karoliina Jalava et al., 2023). This finding was corroborated by multiple large retrospective cohort studies. Drake et al. (2014), analyzing 9,048 patients, found no significant association between in-hospital delay and perforation (OR 1.0, 95% CI 0.99-1.01). Stevenson et al. (2017) reported similar null findings in 955 pediatric patients (OR 1.0 for $\leq$ 24-hour delay, 95% CI 0.96-1.05). Almström et al. (2017) and Teixeira et al. (2012) similarly concluded that in-hospital delays of up to 24 hours did not significantly increase perforation risk.

This discordance between pre-hospital and in-hospital delay effects may be explained by several mechanisms. First, patients who perforate during the pre-hospital phase are biologically distinct, representing a subgroup with either more aggressive disease, delayed immune response, or unique host-pathogen interactions (T. Augustin et al., 2011; Fraz Fahim and Shirjeel, 2005).

Second, upon hospital presentation and diagnosis, multiple interventions including intravenous fluid resuscitation, analgesia, and critically, broad-spectrum antibiotic administration may arrest or retard progression of the inflammatory process (K. Jalava et al., 2021; Salma Abu Foul et al., 2019). Third, modern diagnostic imaging, particularly high-resolution CT, enables accurate identification of uncomplicated appendicitis with negative predictive value exceeding 95%, allowing confident selection of patients appropriate for non-emergent management (S. Musunuru et al., 2007; B. Jeon et al., 2018). Fourth, the time-dependent risk function may be non-linear, with perforation risk plateauing or decelerating after an initial period of disease stabilization under medical care (Laura A. Harmon et al., 2016; Khaled Abdul Jawad et al., 2020).

Population-Specific Risk Modification

While the aggregate evidence supports safety of limited in-hospital delay for unselected adult populations, our stratified analysis reveals critical effect modification by age, clinical presentation, and radiological findings that demands individualized surgical timing decisions.

Pediatric Population

Eleven studies specifically examining pediatric populations demonstrated consistently stronger associations between in-hospital delay and perforation compared to adult cohorts. Meltzer et al. (2016) found that each hour of delay from emergency department triage to incision increased perforation odds by 2% (AOR 1.02, 95% CI 1.00-1.04), with absolute perforation risk increasing from 13% at 0 hours to 22% at 24 hours. Bonadio et al. (2015) reported perforation rates of 0% for surgery within 9 hours, 21% for 9-24 hours, and 41% for delays >24 hours, with estimated odds ratios for perforation increasing from 2.05 at 8 hours to 8.67 at 24 hours. Serres et al. (2017), in an analysis of over 4,000 children, demonstrated that each additional hour of in-hospital delay was associated with 1.8% increased odds of complicated appendicitis.

Several factors may explain this accelerated time-dependent risk in children. The pediatric appendix has a thinner wall and less developed omental coverage, potentially reducing the threshold

for perforation once transmural inflammation develops (Paula Castro et al., 2022; C. Narsule et al., 2011). Children also exhibit less precise localization of pain and atypical presentations, potentially delaying both pre-hospital and in-hospital diagnosis (K. Mandeville et al., 2015; I. Ozguner et al., 2004). Furthermore, the limited physiological reserve in young children may result in more rapid clinical deterioration once perforation occurs (Paulette I. Abbas et al., 2016; G. Frongia et al., 2022). These findings mandate that pediatric appendicitis, even when radiologically uncomplicated, should be prioritized for expeditious surgical intervention with minimal in-hospital delay.

Elderly Population

Six studies specifically examining elderly patients (variably defined as >60, >65, or geriatric populations) consistently demonstrated both higher baseline perforation rates and accelerated time-dependent perforation risk. Hanson et al. (2019) reported that while younger adults with non-perforated appendicitis on admission CT could safely tolerate up to 24-hour delay, patients aged >65 years demonstrated significantly increased perforation risk with delays exceeding 12 hours. F. Rondelli et al. (2019) found that elderly patients had 2.3-fold higher odds of perforation compared to younger cohorts, with each 6-hour increment of in-hospital delay associated with 15% increased perforation risk. Augustin et al. (2011) demonstrated that the effect of delay on perforation was significantly confounded by age, with elderly patients perforating earlier and more frequently despite shorter symptom duration.

The mechanisms underlying this age-dependent vulnerability likely include immunosenescence with blunted inflammatory response leading to delayed presentation, atypical symptomatology masking classic peritoneal signs, greater prevalence of comorbidities confounding clinical assessment, and reduced physiological reserve limiting compensatory responses to progressive inflammation (Chia-Lin Chou et al., 2014; Orhan Üreyen et al., 2022). These findings indicate that elderly patients should be classified as high-priority for urgent appendectomy regardless of initial radiographic classification as uncomplicated.

Appendicolith as High-Risk Marker

Five studies specifically examined the modifying effect of appendicolith on the time-perforation relationship, with remarkably consistent findings. Jeon et al. (2018) demonstrated that patients with CT-confirmed appendicolith were 2.2 times more likely to develop complicated appendicitis within 12 hours of admission compared to those without appendicolith. Prayle et al. (2023) reported that the presence of appendicolith shortened the mean time to perforation from 28 hours to 14 hours, with 34% of appendicolith-positive patients progressing to perforation within 24 hours versus 11% of appendicolith-negative patients. Bonadio et al. (2015) identified appendicolith as the strongest independent predictor of perforation with in-hospital delay (OR 4.2, 95% CI 2.1-8.4).

The pathophysiological basis for this accelerated risk is well-established. Appendicoliths are inspissated fecal concretions that cause obstructive appendicopathy, increasing intraluminal pressure, compromising venous outflow, and promoting rapid bacterial overgrowth and transmural migration (M. Elniel et al., 2018; Jong Wan Kim et al., 2018). Unlike non-obstructive, catarrhal appendicitis which may remain stable for extended periods, obstructive appendicitis follows a more predictable and accelerated progression to perforation (B. Jeon et al., 2016; Hyun Kyu Kim et al., 2016). These findings mandate that patients with radiologically identified appendicolith, regardless of age or clinical severity, should be prioritized for surgery within 12 hours of diagnosis.

Confounding Factors and Analytical Challenges

Our review identified substantial methodological heterogeneity that complicates synthesis and interpretation of the evidence base. A critical source of confounding is the indication bias inherent in observational studies: patients selected for delayed surgery systematically differ from those undergoing immediate appendectomy. Sicker patients, those with equivocal presentations requiring prolonged diagnostic evaluation, and those with greater comorbidity burden may be paradoxically both more likely to experience delay and more likely to perforate, creating spurious

associations in unadjusted analyses (M. Busch et al., 2011; D. Kearney et al., 2008). Conversely, patients with classical presentations and unequivocal examination findings may be prioritized for immediate surgery, while those with atypical symptoms undergo diagnostic imaging and consequently delayed operative intervention (F. T. Drake, 2013; Shuo-Lun Lai et al., 2024).

The use of multivariate regression to address confounding was inconsistent across studies, with substantial variation in covariates selected for adjustment. While most contemporary studies adjusted for age, gender, and white blood cell count, adjustment for critical confounders including symptom duration, fever, C-reactive protein, and antibiotic administration timing was highly variable (Stefano Agnesi et al., 2024; P. Youatou Towo et al., 2012). Only one study employed propensity score matching to address baseline differences between early and delayed surgery groups, representing an important methodological advancement (B. Jeon et al., 2018). Future observational studies should routinely employ such techniques to minimize confounding by indication.

The definition and measurement of waiting time itself represents a fundamental source of heterogeneity. Start points ranged from symptom onset, emergency department triage, hospital admission, diagnosis confirmation, to randomization; end points included surgical booking time, operating room entry, incision time, and anesthesia induction (James A. Meltzer et al., 2016; W. Bonadio et al., 2015a; Ying-xin Wang, 2017). These definitional inconsistencies preclude precise meta-analytic pooling and limit comparative effectiveness assessment across healthcare systems. We strongly recommend adoption of standardized waiting time definitions in future research, specifically distinguishing: (1) total symptom duration (patient delay); (2) door-to-diagnosis time (diagnostic delay); and (3) diagnosis-to-incision time (operative delay). Each phase has distinct determinants, implications, and modifiability.

Secondary Outcomes and Economic Implications

Beyond perforation, our analysis examined secondary outcomes with important implications for patient recovery and healthcare resource utilization. The relationship between in-hospital delay and length of stay was consistently positive across 18 studies, though the clinical significance of this association was debated. Aiken et al. (2020) reported significantly longer hospitalization in patients with >12-hour operative delay (median 2.1 vs 1.6 days, $p < 0.01$), while Ingraham et al. (2010) found statistically significant but clinically modest differences in length of stay. Importantly, several studies demonstrated that the prolonged hospitalization associated with delay was mediated primarily through perforation; when analyses were restricted to patients remaining non-perforated, the association between delay and length of stay attenuated substantially (T. Aiken et al., 2020; Christi Evana Doda et al., 2025). This suggests that efforts to minimize perforation, whether through expedited surgery or effective non-operative management, represent the primary mechanism for reducing hospitalization duration.

Surgical site infection outcomes demonstrated similarly inconsistent associations with in-hospital delay. Teixeira et al. (2012) reported that delay >6 hours was independently associated with increased SSI risk, particularly in non-perforated appendicitis (OR 1.9, 95% CI 1.2-3.0). However, multiple subsequent studies, including the PERFECT trial, found no significant difference in SSI rates between early and delayed surgery groups (Karoliina Jalava et al., 2023; D. Fung et al., 2015; R. Riauka et al., 2018). Wahyuning Ati Ashari et al. (2021), in a narrative review, concluded that the evidence for an independent association between operative delay and SSI, independent of perforation status, remains weak and inconsistent.

Indonesian and Regional Context

This review deliberately incorporated extensive Indonesian and Southeast Asian literature, revealing important regional considerations. Multiple Indonesian studies demonstrated that pre-hospital delay remains the dominant contributor to perforation in this setting, with symptom duration exceeding 48 hours in 44-72% of perforated cases (S. M. A. Hakim et al., 2018; Alvian Rachman Santosa et al., 2025; Nurnadhirah Mirantika et al., 2021). Contributing factors include

geographic barriers to healthcare access, limited public awareness of appendicitis symptoms, reliance on traditional medicine, and primary care level diagnostic challenges (Irmayanti Johar Bima et al., 2021; Akhmad Kheru et al., 2022). These findings underscore that interventions to reduce perforation in low-resource and geographically dispersed populations must prioritize public education and primary care capacity building rather than solely focusing on in-hospital surgical delays.

Furthermore, several Indonesian studies examined the diagnostic and prognostic utility of readily available laboratory parameters in risk stratification. Febria Valentine Aritonang et al. (2022) and Festy Ladyani and Dewi (2019) demonstrated that leukocyte counts significantly differ between non-perforated and perforated appendicitis, though with substantial overlap limiting discriminatory utility. Prita Aulia M Selomo (2021) and I. W. Wismaya et al. (2019) reported that neutrophil-lymphocyte ratio offers superior predictive performance for perforation, representing an accessible, low-cost tool for risk stratification in settings where CT imaging is not routinely available. These findings have important implications for resource-appropriate clinical pathway development in Indonesian healthcare facilities.

CONCLUSION AND RECOMMENDATIONS

Summary of Key Findings

This comprehensive systematic review of 89 studies examining the relationship between surgical waiting time and appendiceal perforation yields several definitive conclusions. First, pre-hospital delay (symptom duration prior to presentation) demonstrates a consistent, robust, dose-dependent positive association with perforation risk at presentation. This relationship is among the most firmly established findings in acute appendicitis literature and mandates continued emphasis on public education and healthcare access to minimize patient delay.

Second, the association between in-hospital delay (time from presentation to surgery) and perforation among patients initially presenting with uncomplicated appendicitis is substantially

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weaker, inconsistent across studies, and significantly modified by patient characteristics. For non-elderly adults without high-risk features, a surgical window of up to 24 hours from presentation does not appear to significantly increase perforation risk, particularly when preoperative antibiotics are administered. This finding supports the safety of scheduled, non-emergent appendectomy for carefully selected patients and has important implications for operating room resource allocation and surgical workforce optimization.

Third, specific patient subpopulations demonstrate accelerated time-dependent perforation risk and warrant prioritized surgical intervention. These include: (a) pediatric patients, particularly those under 12 years, in whom every hour of in-hospital delay incrementally increases perforation probability; (b) elderly patients (>60-65 years), who exhibit both higher baseline perforation rates and more rapid progression; and (c) patients with radiologically identified appendicolith, who face 2.2-fold increased risk of progression to complicated appendicitis within 12 hours. Additionally, patients presenting with marked inflammatory response (fever $>38.5^{\circ}\text{C}$, WBC $>15,000/\mu\text{L}$, or elevated CRP) should be considered high-risk for time-dependent perforation.

Fourth, the considerable heterogeneity in waiting time definitions, perforation diagnostic criteria, and analytical approaches across the literature impedes precise quantitative synthesis and limits development of universally applicable time thresholds. Standardization of these definitions represents an urgent priority for the field.

Clinical Recommendations

Based on the synthesized evidence, we propose the following risk-stratified approach to surgical timing in acute appendicitis:

1. **Low-risk adult population** (age 18-60 years, no appendicolith, normal or mildly elevated inflammatory markers, hemodynamically stable): Appendectomy can be safely scheduled within 24 hours of diagnosis. This window accommodates overnight delays, optimization of comorbid conditions, and efficient operating room utilization.

2. **High-risk populations requiring urgent appendectomy** (target within 12 hours, ideally sooner): This category includes all pediatric patients (<18 years), elderly patients (>60 years), patients with CT-confirmed appendicolith regardless of age, and patients with significant fever (>38.5°C) or marked leukocytosis (>15,000/ μ L). These patients should be prioritized on emergency operating lists.
3. **Patients with established perforation at presentation:** These patients require appropriate resuscitation, antibiotic therapy, and timely but not necessarily emergent surgical intervention. Source control remains essential, but the urgency is moderated by physiological optimization.
4. **Pre-hospital delay reduction:** Healthcare systems and public health authorities should implement educational initiatives to improve public recognition of appendicitis symptoms and reduce barriers to timely healthcare seeking, particularly in underserved and geographically remote populations.

Research Recommendations

Priority areas for future investigation include: (1) prospective validation of composite risk stratification models incorporating clinical, laboratory, and radiological parameters to predict individual patient-specific safe waiting windows; (2) randomized controlled trials comparing different in-hospital delay thresholds in high-risk populations, particularly children and the elderly, to establish evidence-based time-to-surgery targets; (3) investigation of optimal antibiotic regimens and durations during the preoperative waiting period to maximize disease stabilization; (4) health economic analyses examining the cost-effectiveness of risk-stratified surgical timing protocols compared to universal emergency appendectomy; (5) development and validation of standardized waiting time definitions and reporting guidelines to enhance comparability across future studies; and (6) implementation science research examining barriers and facilitators to adoption of risk-stratified appendicitis management protocols across diverse healthcare settings.

Concluding Statement

The relationship between surgical waiting time and appendiceal perforation is neither simple nor uniform. The traditional maxim that "time is perforation" requires refinement to "time is perforation for some, in some phases, under some conditions." The critical task for contemporary surgeons and healthcare systems is not to eliminate all surgical delay—an impossible and potentially unnecessary objective—but rather to accurately identify which patients require immediate operative intervention and in whom a defined waiting period may be safely accommodated. Through risk-stratified, evidence-based surgical timing, we can simultaneously optimize individual patient outcomes and health system performance.

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