Annals of Surgery Publish Ahead of Print
DOI:10.1097/SLA.0000000000005996

Delayed vs. Early Laparoscopic Appendectomy (DELAY) for Adult Patients with Acute Appendicitis: A randomized controlled trial

Running Head: The DELAY Randomized Controlled Trial

Authors: Sunil V. Patel MD (1), Lisa Zhang MD (1,2), Zuhaib M. Mir (1), Madeline Lemke (3), William R. Leeper (3), Laura J. Allen (3), Eric Walser (3), Kelly Vogt (3)

Affiliations:

1. Department of Surgery, Queen's University
   Victory 3
   Kingston General Hospital
   76 Stuart Street
   Kingston, Ontario, Canada
   K7L 2V7
2. Department of Surgery, University of Ottawa
   The Ottawa Hospital - General Campus
   501 Smyth Road
   Ottawa, Ontario, Canada
   K1H 8L6
3. Department of Surgery, Western University
   339 Windermere Road
   London, Ontario, Canada
   N6A 5A5

Corresponding Author:
Sunil Patel
Department of Surgery, Queen's University
Victory 3
Kingston General Hospital
76 Stuart Street
Kingston, Ontario, Canada
Email: Sunil.Patel@KingstonHSC.ca

Keywords: appendectomy, appendicitis, after-hours care, postoperative complications, emergency surgery

Competing or Conflicts of Interests: There are no competing or conflicts of interests to declare for any of the authors.

Funding: None

Manuscript Word Count: 2886
Abstract Word Count: 349

Mini-Abstract

This non-inferiority trial compared delayed vs. immediate surgery for those with acute appendicitis. Delayed appendectomy was not inferior to immediate surgery (risk difference -12.2%, 95%CI -24.4% to +0.4%, test of non-inferiority $p < 0.0001$). Delayed appendectomy is a viable alternative to immediate surgery in those with acute appendicitis.

Abstract (241 Words)

Objective: To assess whether delaying appendectomy until the following morning is non-inferior to immediate surgery in those with acute appendicitis presenting at night.

Background: Despite a lack of supporting evidence, those with acute appendicitis who present at night frequently have surgery delayed until the following morning.

Methods: The delay trial is a non-inferiority randomized controlled trial conducted between 2018 – 22 at two tertiary care hospital in Canada. Adults with imaging confirmed acute appendicitis who presented at night (2000 – 0400). Delaying surgery until after 0600 was compared with immediate surgery. The primary outcome was 30 day post operative complications. An *a prior* non-inferiority margin of 15% was deemed clinically relevant.

Results: 127 of a planned 140 patients were enrolled in the DELAY trial (59 in the delayed group, 68 in the immediate group). The two groups were similar at baseline. The mean time between decision to operate and surgery was longer in the delayed group (11.0 hours vs. 4.4 hours, $p < 0.0001$). The primary outcome occurred in 6/59 (10.2%) of those in the delayed group vs. 15/67 (22.4%) of those in the immediate group ($P = 0.07$). The difference between groups met the *a priori* non-inferiority criteria of +15% (risk difference -12.2%, 95%CI -24.4% to +0.4%, test of non-inferiority $p < 0.0001$).

Conclusions and Relevance: The DELAY study is the first trial to assess delaying appendectomy in those with acute appendicitis. We demonstrate non-inferiority of delaying surgery until the following morning.

Trail Registration: This trial was registered with *ClinicalTrials.gov* (NCT03524573).

Introduction

Acute appendicitis is a frequent indication for emergency abdominal surgery.(1) It is commonly believed that the severity of appendicitis increases as time elapses, with increasing risk of perforation occurring without timely intervention. (2) Immediate surgical intervention is the traditional proposed standard of care for these patients. However, other considerations such as resource limitations overnight and the safety of nighttime operating, have resulted in an alternate strategy of delaying surgery until the following morning for those with acute appendicitis. Multiple large retrospective studies have shown that variation in surgical practice exists in terms of delaying appendectomy, despite a lack of level 1 evidence supporting this practice.(3-6)

The currently availably observational data remain inconclusive with respect to the safety of delaying appendectomy. Several retrospective studies have suggested an association between delay to treatment and perforation, with perforation leading to poorer outcomes including more advanced pathology, intra-abdominal abscess, increased length of antibiotic therapy, greater post-operative complications, increased length of hospital stay, and higher cost.(7-11) Several more recent studies have challenged these findings, and have not demonstrated worse outcomes when appendectomy is performed 12 – 24 hours after presentation or when it is delayed until morning when a patient presents at night. (4, 12-16) Our group previously reported an increase in postoperative complications following appendectomy only after a delay of > 24 hours from triage at the emergency department to surgery. (17)

When performing an urgent operative intervention one must also consider the potential risk of nighttime operating. Sleep deprivation and fatigue have been associated with increased technical errors.(18) Several studies examining the safety of nighttime operating have yielded

mixed results. Some have identified that nighttime operating is associated with complications, increased rate of conversion to open surgery, more returns to the operating room, and/or longer length of hospital stay. (19-21) However, some of the same studies also showed no increase in overall complications with nighttime operating.(20, 21) In our previous population level study assessing those with acute appendicitis, we found that there was no increased risk of operating at night compared to day time operating, when adjusted for time from triage to surgery. (17)

Prior to this work, there was a lack of level 1 evidence supporting the practice of delaying appendectomy until the following morning in those who present at night. Thus, the objective of this randomized controlled trial was to determine if delaying appendectomy was non-inferior with respect to the incidence of post-operative complications, when compared to immediate surgery in those with acute appendicitis.

Methods

The protocol for this study was previously published (22) and was registered with clinical trials.gov (NCT03524573). The study is reported as per the CONSORT recommendations for reporting of randomized controlled trials. (23)

Study Design, Participants and Setting

The study was a non-inferiority, prospective, two-armed randomized controlled trial comparing delayed appendectomy (intervention: surgery after 0600 the morning following decision to operate) to immediate appendectomy (control: appendectomy between 2000 and 0400 and within 6 hours of decision to operate). The study was conducted at two tertiary care Canadian hospitals with established and mature acute care surgical services and dedicated daytime emergency surgery operative time.

All adult patients who presented with a diagnosis of acute appendicitis, confirmed with imaging (computed tomography or ultrasound), in whom the expected time of operation was between 2000 and 0400 were eligible for inclusion. Only those being considered for operative management were eligible for this study. The expected time of operation was required to be within 6 hours of the decision to operate to ensure those in the immediate appendectomy group could achieve timely operative intervention. The exclusion criteria were: hemodynamic instability (HR > 100 beat/minute, SBP < 90 mmHg), sepsis, diagnostic uncertainty, presence of abscess on imaging, pregnancy, patients who were not surgical candidates (as defined by the surgeon), patients where the surgeon feels it is unsafe to delay operation, and patients who were unable to sign consent. In addition, patients were ineligible for inclusion if operating room time was unavailable the following morning, or if timely operating room time (i.e. within 6 hours of the decision to operate) was unavailable.

Intervention and management

Participants randomized to the control arm underwent "immediate" appendectomy within 6 hours of the decision to operate. Participants in the "delayed" appendectomy were admitted to hospital, with a plan for appendectomy to occur after 0600 the following morning. Regardless of the allocation, participants were given intravenous antibiotics at the time of admission with re-dosing in the operating room if appropriate. In addition, participants received fluid resuscitation and other interventions as deemed appropriate by the surgical team. As per the standard of care at the participating institutions, all individuals were to undergo appendectomy regardless of their response to IV antibiotics (i.e. non-operative management was not offered after enrollment).

After surgery, participants received standard postoperative care and were discharged as per usual criteria. In general, postoperative appendectomy patients were permitted to resume diet after surgery and typically discharged by postoperative day one. Ongoing antibiotics were not routinely offered post operatively, except at the discretion of the surgeon based on appendiceal perforation and/or intraabdominal contamination.

Outcome Measures

The primary outcome was the 30-day post operative complication rate, defined as a composite of: mortality, readmission to hospital, emergency department visit, percutaneous drain insertion, reoperation, prolonged hospital stay (>7 days), and postoperative complications (including cardiac, ileus/bowel obstruction, neurologic, venous thromboembolism, pneumonia, other respiratory, surgical site infection, urinary tract infection, and other complications). This definition was used in our previous work assessing postoperative complications in those with acute appendicitis. (17, 24) Secondary outcomes included appendiceal perforation at time of surgery and operative length of time.

Randomization, Allocation, Blinding and Follow Up

Simple randomization was conducted using computer-based randomization (Microsoft Excel, Microsoft Corporation). Sequentially numbered, opaqued envelopes were used. Once a patient was deemed eligible for participation and agreed to be enrolled, the surgical team opened the envelope to determine the treatment arm. Due to the nature of the investigation, neither the surgical team nor the participants were blinded to the intervention. All participants were offered a follow up appointment (either clinic visit or telephone visit) at 30 days. Study outcomes were assessed and recorded at 30 days by a member of the research who was blinded to the allocation group.

Sample Size Calculation

Based on our previous population level studies, as well as other large studies assessing post operative complications in acute appendicitis we hypothesized the complication rate to be 14% in the control (immediate) group. (3, 6, 15, 24) A non-inferiority margin of 15% was selected based on clinical significance, and based on our previous work assessing complication and delays in those undergoing appendectomy. (17) Based on a power of 80% and an α of 5%, we determined that 134 individuals (67 in each arm) were needed. To account for a 5% loss to follow up, we aimed to enroll 140 individuals. Our previously published protocol (22) initially described a total sample size of 128, which was based on assumptions that were revised during the ethics approval process.

Statistical Analysis

This study was analyzed by intention-to-treat (ITT) analysis. A secondary analysis of the primary outcome analyzed per-protocol was also conducted. The following variables were

included to provide baseline comparison between the intervention and control groups: age, sex, ASA class, white blood count, temperature at presentation, CT or ultrasound diagnosis, and perforation status on imaging. Baseline characteristics are presented as total number per group with percentages for categorical variables and means with standard deviations for continuous variables.

For the primary outcome, the proportions of patients who experienced a complication were calculated for each group and compared using Chi-square test. Risk difference and 95% confidence interval were also calculated and reported with the control group as the referent group. If the bounds of the 95%CI interval were entirely below the *a priori* non-inferiority margin (i.e. a 15% increased risk of complications in the delay group) then non-inferiority would be concluded. If the 95% confidence interval crossed the non-inferiority margin, then non-inferiority will not have been proven.

Secondary outcomes were reported as absolute number with percentage and compared using Chi-square or Fisher's Exact Test for categorical variables. Continuous variables were reported as means (with standard deviations) and medians with interquartile range. Means were compared using t-test. Missing data was expected to be minimal as all data required is easily accessible via the electronic medical record and the follow up period is only 30 days. Data analysis was limited to those who completed 30 day follow up.

All statistical analyses were conducted with STATA (ver. 12 or later).

Results

This randomized controlled trial aimed to recruit a total of 140 individuals. This study was terminated prematurely after a total of 127 (91%) individuals were recruited. The study was closed early due to significant changes in operating room resources available at one site. Due to

the significant surgical backlog as a consequence of the COVID-19 pandemic, access to reliable day time emergency surgery operative time was eliminated. This resulted in the inability to accrue patients.

A total of 127 individuals were randomized to either delayed surgery (n = 59) or immediate surgery (n = 68). Of those allocated to the delayed group, 2 underwent immediate surgery (within 6 hours of the decision to operate and prior to 0600 the next morning). Of those allocated to immediate surgery, 8 underwent delayed surgery (>6 hours from the decision to operate and after 0600 the next morning), while 1 was lost to follow up. Thus, for the intention to treat analysis, there were 59 individuals in the delayed group and 67 in the immediate group. For the per protocol analysis, there were 65 in the delayed group and 62 in the immediate group. (Figure 1)

Those allocated to the delayed vs. immediate surgery groups were similar in age, sex, American society of anesthesiology (ASA) score, mean white blood cell count and mean temperature. The majority of individuals were diagnosed using computed tomography, with few having radiologic evidence of perforated appendicitis (3.9% of the total cohort). (Table 1)

The groups were also similar in time between onset of symptoms and decision to operate. In both groups, most individuals presented more than 18 hours after onset of symptoms (69.5% in the delay group and 77.6% in the immediate group, $p = 0.57$). As expected, those who were randomized to the delayed group had a longer mean and median time between the decision to operate and the surgical start time (mean 11.0 hours vs. 4.4 hours, $p < 0.0001$; median 11.0 hours vs. 3.5 hours). The risk of conversion to open surgery was low in both groups (1.7% and 2.9%, $p = 0.65$), with similar mean and median operative times between groups (mean 48.9 minutes

delayed vs 53.5 minutes immediate, p = 0.23; median 44 minutes delayed vs. 49 minutes immediate). (Table 2)

Outcomes

The primary outcome, which was a composite of 30 day post operative complications, occurred in 6/59 (10.2%) of those in the delay group and 15/67 (22.4%) in the immediate group (p = 0.07). Comparing the delayed group to the immediate group, the risk difference was -12.2% (95%CI -24.8% to +0.4%), favouring the delay group. Testing our non-inferiority margin of +15%, we demonstrated non-inferiority between groups (p < 0.001). (Table 3, Figure 2)

Within our composite, the most common complication was return to the emergency department which was seen in 4/59 (6.8%) in the delay group and 12/67 (17.9%) in the immediate group. There were no mortalities, reoperation or percutaneous drain insertions in either group. There was also a low risk of re-admission to hospital (3.4% in the delay group, 3.0% in the immediate group) and prolonged admission > 7 days (1 patient in the immediate group).

A per-protocol analysis was completed, analyzing those who crossed over in the per protocol treatment groups. This analysis demonstrated superiority of the delayed approach (5/65, 7.7% vs. 16/61, 26.2%, p = 0.005).

Discussion

The DELAY study is the first randomized trial to assess whether delaying surgery is non-inferior to immediate surgery in those with acute appendicitis who present at night. We demonstrated that delaying surgery was non-inferior to immediate surgery. We also found in the per-protocol analysis, that delaying surgery was superior to immediate surgery as demonstrated by a significant reduction in postoperative complications (7.7% vs. 26.2%, p = 0.005). This was

primarily driven by the complication of return visit to the emergency department. The results of this study are directly applicable to those who manage acute appendicitis, and supports the commonly utilized management strategy of delaying operative intervention until the morning.

Strengths and Weaknesses

The strength of this study is in the design. This is a randomized controlled trial with computer generated random sequence generation, allocation concealment, blinding of the outcome assessors, low rates of loss to follow up (1/127, <1%), with a registered and published study protocol.(22) The non-inferiority design was appropriate and selected to demonstrate that delaying surgery is an acceptable alternative to the standard of care of immediate surgery. We used a clinically significant non-inferiority margin, using a hypothesized complication risk based on previously published population data from similar settings. (17, 24) The hypothesized complication risk was 14% compared with the overall observed risk of 16.7% (n = 21/126). The primary weakness of this work was the requirement to stop early. Our original sample size calculation required 134 participants (67 per group) with complete follow up, and we enrolled 127 with 126 who completed follow up (94% of the intended enrollment). Sensitivity analysis (assuming that enrollment was complete and that all remaining individuals in the delay group experienced the primary outcome) still demonstrates non-inferiority (risk difference -1.4%, 95%CI -15.4% to +12.5%, test of non-inferiority margin of +15%: p = 0.04). Thus, we can confidently conclude that the non-inferiority threshold was met.

Other weaknesses of this study included the inability to blind the patient or the surgery team due to the nature of the intervention. In addition, a total of 10 participants crossed over between interventions (8 from the immediate group and 2 from the delayed group). This cross over represents the real world experience of the participating centres. Emergency surgical time,

especially at night, is a shared resource. Those in the immediate group were delayed due to other more emergent cases being prioritized. Finally, our primary outcome is a composite of 30 day complications. This was selected based on previous population based studies. At the present time there is no validated, commonly agreed upon outcome, and this represents a clinically relevant one.

Study Results in Relation to Previous Publications

The risks of appendectomy at a population level have previously been reported by our group.(24) Using the same definition, this study reported a risk of 29%, with the most common complication being return to the emergency department. The current trial found a lower risk of complication for the entire group (21/126, 17%), but also found that emergency department visits were the most common complication.

Nearly all prior studies assessing delayed appendectomy were observational, or meta-analyses of observational studies. We previously published a population level study on risks with delayed surgery in Ontario.(17) This study demonstrated an increased risk of complications only after a delay of > 24 hours (OR 1.27, 95%CI 1.14 – 1.43 vs. <6 hour delay 1, [ref]). This trial uses the same composite outcome definition as the population level study. Other works have also found no difference in delaying appendectomy. Similar findings were reported in a previous American study using the national surgical quality improvement program (NSQIP) data. Ingraham et al. (4) found no significant difference in the adjusted rates of overall 30 day morbidity when comparing <6 hours delay (5.5%) vs. 6-12 hours (5.4%) vs. >12 hours (6.1%). Notably, there was also no difference found in serious morbidity/mortality either. Their morbidity rates were lower than what was reported in this trial; however, it must be noted that their data was collected retrospectively from a database and only included SSI, pneumonia, UTI,

DVT, peripheral neuropathy, and unplanned intubation in their definition of morbidity, while our morbidity definition was more inclusive and our data was collected prospectively. A number of additional studies have also found little difference in delaying surgery, based on observational data. (14-16) A 2018 meta-analysis of 21 studies (20 observational, 1 RCT) published between 1997-2018 (54,435 patients) found no difference between time to surgery (<6 hours, 6-12 hours, > 12 hours) and either complicated appendicitis or SSI rate. (25) Notably, this meta-analysis found that delays > 24 hours did result in higher risks to the patient.

Meaning and Implications of the Study

The present study demonstrates non-inferiority of delaying appendectomy in those with acute appendicitis. Although much has been hypothesized on the implications of delaying surgery in those with acute appendicitis due to lack of source control and potential for progression to perforated and/or gangrenous appendicitis, these concerns do not seem to be justified. Our results support previous population studies that have demonstrated delaying appendectomy for up to 12 – 24 hours is safe. In the per-protocol analysis, we demonstrate that delaying appendectomy was *superior* to immediate surgery. The mechanism for this was not explicitly assessed. One hypothesis is fatigue of the health care team, which may have contributed. An additional hypothesis is the difference in communication between the health care team and the patient at night. The most common complication in our study was return to the emergency department (but not readmission). It was proposed that better communication occurs during daytime hours which may prevent unnecessary emergency department visits.

The DELAY study provides level 1 evidence of non-inferiority in delaying appendectomy until morning in those with acute appendicitis who present at night. The practice

of delaying surgery has been adopted in a number of settings, and this study support this change in practice.

Acknowledgements

Author Contributions: All authors approved the final version of this manuscript and made substantive contributions as defined by the International Committee of Medical Journal Editors (ICMJE). SVP and LZ conceptualized the design of the work; SVP, LZ, ZMM, ML, WRL, EW, KV acquired the data; SVP analyzed the data; all authors contributed to the interpretation of the data; All authors contributed to either the drafting or revising of this manuscript; All authors agree to be accountable for this work.

The authors have no relevant conflicts of interest to declare.

We would like to acknowledge the following individuals for identifying and/or recruiting eligible patients to the study:

Dr. Sean Bennett, MD (1); Dr. Antonio Caycedo, MD (1); Dr. C. Jay Engel, MD (1), Dr. Diederick Jalink, MD (1), Dr. P. Hugh MacDonald, MD (1), Dr. Shaila Merchant, MD (1), Dr. Sulaiman Nanji, MD (1), Dr. David Robertson, MD (1), Dr. Ross Walker, MD (1), Dr. Boris Zevin, MD (1). Dr. Muriel Brackstone (2), Dr. Alison MacIver (2), Dr. Steven Latosinsky (2), Dr. Ken Leslie (2), Dr. Michael Ott (2), Dr. Terry Zweip (2), Dr. Brad Moffat (2), Dr. Neil Parry (2), Dr. Darryl Gray (2), Dr. Rich Hilsden (2).

(1) Department of Surgery Kingston Health Sciences Centre, Kingston, Ontario, Canada

(2) Department of Surgery, London Health Science Centre, London, Ontario, Canada

References

1. Pfuntner A, Wier LM, Stocks C. Most Frequent Procedures Performed in U.S. Hospitals, 2010. Healthcare Cost and Utilization Project (HCUP) Statistical Briefs. Rockville (MD): Agency for Healthcare Research and Quality (US); 2006.
2. Temple CL, Huchcroft SA, Temple WJ. The natural history of appendicitis in adults. A prospective study. Annals of surgery. 1995;221(3):278-81.
3. Boomer LA, Cooper JN, Anandalwar S, Fallon SC, Ostlie D, Leys CM, et al. Delaying Appendectomy Does Not Lead to Higher Rates of Surgical Site Infections: A Multi-institutional Analysis of Children With Appendicitis. Annals of surgery. 2016;264(1):164-8.
4. Ingraham AM, Cohen ME, Bilimoria KY, Ko CY, Hall BL, Russell TR, et al. Effect of delay to operation on outcomes in adults with acute appendicitis. Archives of surgery (Chicago, Ill : 1960). 2010;145(9):886-92.
5. Jeon BG, Kim HJ, Jung KH, Lim HI, Kim SW, Park JS, et al. Appendectomy: Should it Be Performed So Quickly? The American surgeon. 2016;82(1):65-74.
6. Jung JW, Park J, Jeon GJ, Moon YS, Yang SY, Kim TO, et al. The Effectiveness of Personalized Bowel Preparation Using a Smartphone Camera Application: A Randomized Pilot Study. Gastroenterology research and practice. 2017;2017:4898914.
7. Bickell NA, Aufses AH, Jr., Rojas M, Bodian C. How time affects the risk of rupture in appendicitis. Journal of the American College of Surgeons. 2006;202(3):401-6.
8. Ditillo MF, Dziura JD, Rabinovici R. Is it safe to delay appendectomy in adults with acute appendicitis? Annals of surgery. 2006;244(5):656-60.
9. Kearney D, Cahill RA, O'Brien E, Kirwan WO, Redmond HP. Influence of delays on perforation risk in adults with acute appendicitis. Diseases of the colon and rectum. 2008;51(12):1823-7.
10. Papandria D, Goldstein SD, Rhee D, Salazar JH, Arlikar J, Gorgy A, et al. Risk of perforation increases with delay in recognition and surgery for acute appendicitis. The Journal of surgical research. 2013;184(2):723-9.
11. Reid RI, Dobbs BR, Frizelle FA. Risk factors for post-appendicectomy intra-abdominal abscess. The Australian and New Zealand journal of surgery. 1999;69(5):373-4.
12. Eko FN, Ryb GE, Drager L, Goldwater E, Wu JJ, Counihan TC. Ideal timing of surgery for acute uncomplicated appendicitis. North American journal of medical sciences. 2013;5(1):22-7.
13. Kim HK, Kim YS, Lee SH, Lee HH. Impact of a Delayed Laparoscopic Appendectomy on the Risk of Complications in Acute Appendicitis: A Retrospective Study of 4,065 Patients. Digestive surgery. 2017;34(1):25-9.
14. Kim SH, Park SJ, Park YY, Choi SI. Delayed Appendectomy Is Safe in Patients With Acute Nonperforated Appendicitis. International surgery. 2015;100(6):1004-10.
15. Shin CS, Roh YN, Kim JI. Delayed appendectomy versus early appendectomy in the treatment of acute appendicitis: a retrospective study. World journal of emergency surgery : WJES. 2014;9(1):8.
16. Surana R, Quinn F, Puri P. Is it necessary to perform appendicectomy in the middle of the night in children? BMJ (Clinical research ed). 1993;306(6886):1168.
17. Patel SV, Groome PA, S JM, Lajkosz K, Nanji S, Brogly SB. Timing of surgery and the risk of complications in patients with acute appendicitis: A population-level case-crossover study. The journal of trauma and acute care surgery. 2018;85(2):341-7.

18. Eastridge BJ, Hamilton EC, O'Keefe GE, Rege RV, Valentine RJ, Jones DJ, et al. Effect of sleep deprivation on the performance of simulated laparoscopic surgical skill. American journal of surgery. 2003;186(2):169-74.
19. Phatak UR, Chan WM, Lew DF, Escamilla RJ, Ko TC, Wray CJ, et al. Is nighttime the right time? Risk of complications after laparoscopic cholecystectomy at night. Journal of the American College of Surgeons. 2014;219(4):718-24.
20. Turrentine FE, Wang H, Young JS, Calland JF. What is the safety of nonemergent operative procedures performed at night? A study of 10,426 operations at an academic tertiary care hospital using the American College of Surgeons national surgical quality program improvement database. The Journal of trauma. 2010;69(2):313-9.
21. Wu JX, Nguyen AT, de Virgilio C, Plurad DS, Kaji AH, Nguyen V, et al. Can it wait until morning? A comparison of nighttime versus daytime cholecystectomy for acute cholecystitis. American journal of surgery. 2014;208(6):911-8; discussion 7-8.
22. Zhang L, Lemke M, Mir ZM, Patel SV. Delayed vs. Early Appendectomy (DELAY) trial for adult patients with acute appendicitis: Study protocol for a randomized controlled trial. Contemporary clinical trials. 2021;102:106288.
23. Piaggio G, Elbourne DR, Pocock SJ, Evans SJ, Altman DG. Reporting of noninferiority and equivalence randomized trials: extension of the CONSORT 2010 statement. Jama. 2012;308(24):2594-604.
24. Patel SV, Nanji S, Brogly SB, Lajkosz K, Groome PA, Merchant S. High complication rate among patients undergoing appendectomy in Ontario: a population-based retrospective cohort study. Canadian journal of surgery Journal canadien de chirurgie. 2018;61(6):412-7.
25. Li J, Xu R, Hu DM, Zhang Y, Gong TP, Wu XL. Effect of Delay to Operation on Outcomes in Patients with Acute Appendicitis: a Systematic Review and Meta-analysis. Journal of gastrointestinal surgery : official journal of the Society for Surgery of the Alimentary Tract. 2019;23(1):210-23.

Figure 1: CONSORT Flowsheet of included participants

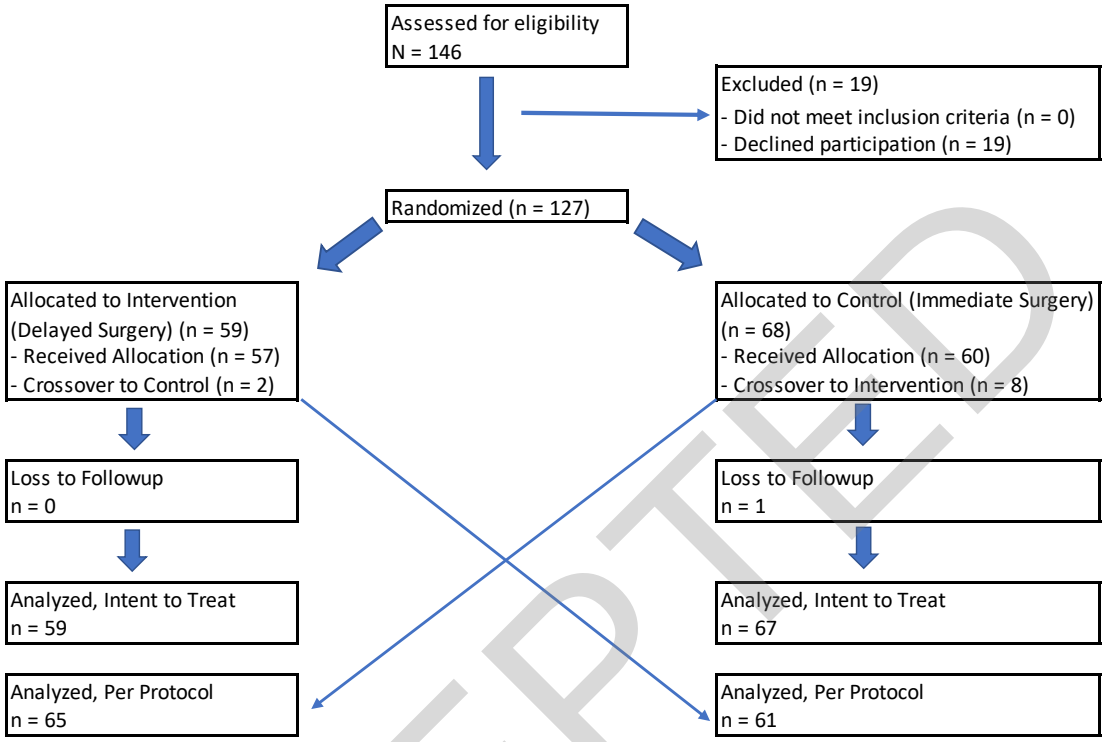

Figure 2: Non-inferiority assessment

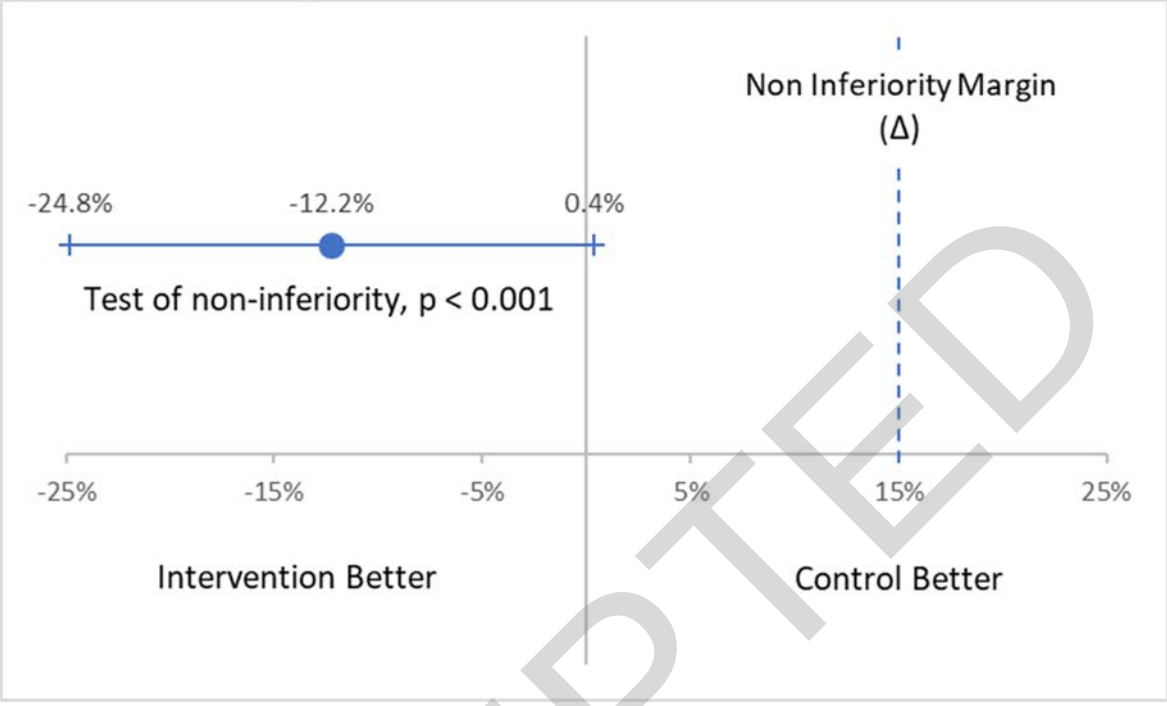

Table 1: Characteristics of included participants based on allocations

Characteristic	Intervention (Delayed Surgery) (n = 59)	Control (Immediate Surgery) (n = 68)	
Mean Age (STD)	42.2 (17.0)	38.9 (16.7)	P = 0.27
Sex			
Male (%)	26 (44.1%)	34 (50.0%)	P = 0.50
Female (%)	33 (55.9%)	24 (50.0%)	
ASA			
Class I	8 (13.8%)	12 (17.9%)	P = 0.81
Class II	20 (34.5%)	20 (29.9%)	
Class III	28 (48.3%)	31 (46.3%)	
Class IV	2 (3.5%)	4 (6.0%)	
Mean White Blood Cell Count (STD)	13.3 (3.9)	12.9 (4.1)	P = 0.51
Mean Temperature (STD)	36.9 (0.6)	37.1 (0.5)	P = 0.16
Diagnostic Imaging Test			
Computed Tomography	47 (79.7%)	45 (66.1%)	P = 0.10
Ultrasound	11 (18.6%)	23 (33.8%)	
Both	1 (1.7%)	0 (0%)	
Perforation on Imaging	2 (3.4%)	3 (4.4%)	P = 0.77

Table 2: Treatment Characteristics Based on Allocation

Characteristic	Intervention (Delayed Surgery) (n = 59)	Control (Immediate Surgery) (n = 68)	
Symptom onset to decision to operate			
6 - 12 hours	3 (5.1%)	3 (4.5%)	P = 0.57
12 - 18 hours	15 (25.4%)	12 (17.9%)	
> 18 hours	41 (69.5%)	52 (77.6%)	
Mean Time between decision to operate and surgery, hours (STD)	11.0 (3.6)	4.4 (3.0)	P < 0.0001
Median Time between decision to operate and surgery, hours (IQR)	11.0 (8.6 - 13.3)	3.5 (2.0 - 6.2)	
Conversion to Open	1 (1.7%)	2 (2.9%)	P = 0.65
Mean Operative Time, minutes (STD)	48.9 (21.2)	53.5 (21.0)	P = 0.23
Median Operative Time, minutes (IQR)	44 (35 – 55)	49 (40 – 60)	

Table 3: Primary outcome and secondary outcomes

Characteristic	Delayed Surgery	Immediate Surgery	
Composite Primary Outcome	6/59 (10.2%)	15/67 (22.4%)	P = 0.07 Test of non-inferiority: p < 0.001
Risk Difference, 95% Confidence Interval	-12.2%, -24.4% to + 0.4%	[Ref]	
Specific Complications			
Readmission	2/59 (3.4%)	2/67 (3.0%)	P = 0.90
Emergency Department Visit	4/59 (6.8%)	12/67 (17.9%)	P = 0.06
Length of Stay > 7 days	0 /59(0%)	1/67 (1.5%)	P = 0.35
Other Complications	3/59 (5.1%)	7/67 (10.8%)	P = 0.25
Perforated Appendicitis at Time of Surgery	10/58 (17.2%)	13/68 (19.1%)	P = 0.79
Per Protocol Analysis Composite Primary Outcome	5/65 (7.7%)	16/61 (26.2%)	P = 0.005