

Delay Between Onset of Symptoms and Surgery in Acute Appendicitis Increases Perioperative Morbidity: A Prospective Study

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Abstract

Background Despite significant progress in surgery, controversy persists about timing of appendectomy. Objective of this prospective observational study was to determine associations between time interval from onset of symptoms in appendicitis to appendectomy and postoperative complications.

Methods After institutional review board approval, all adult consecutive patients subjected to emergency appendectomy between 1/9/2013 and 1/12/2014 were prospectively enrolled. Data collection included demographics, open vs. laparoscopic appendectomy, comprehensive complication index (CCI), and 30-day follow-up. To determine time-dependent associations between delay of surgery and complications all patients were stratified into subgroups based on 12-h time intervals from onset of abdominal pain to surgery. Primary outcome was complications per CCI in correlation to delay from symptoms to appendectomy. Secondary outcomes included duration of surgery, hospital length of stay (HLOS), and incidence of complication within 30-day follow-up.

Results A total of 266 patients with a mean age of 35.4 ± 14.8 years met inclusion criteria. Overall, 83.1 % of patients were subjected to laparoscopic appendectomy. Delay to surgery in 12-h increments showed stepwise-adjusted increase in complications per CCI (adj. $P = 0.037$). Also, delay to appendectomy increased significantly duration of surgery and HLOS, respectively (adj. $P < 0.001$ and adj. $P < 0.001$). Overall, 5.7 % of patients developed a surgical site infection after hospital discharge.

Conclusion Extended time interval from the onset of initial symptoms to appendectomy is associated with increased complications per CCI, duration of surgery, and HLOS in acute appendicitis. Prompt appendectomy in acute appendicitis is warranted.

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Introduction

Appendectomy is the most frequently performed emergent abdominal operation with a lifetime risk of appendicitis at 9 % [1, 2]. Despite significant advancements in surgery and antimicrobial therapy, many controversies in the management of acute appendicitis persist.

Many studies have observed that the risk of perforation is time-dependent and extended time to surgery results in poor outcomes [3, 4]. However, other investigations have reported that spontaneous resolution of low-grade appendicitis is common and nonoperative management in these instances may result in good outcomes [5, 6]. Given the

paucity of data, we set out to determine prospectively the relationship between time interval from onset of symptoms to surgery and incidence of complications while comparing disease severity per histology in all specimens.

Methods and patients

Following institutional review board approval, all consecutive patients ≥ 18 years of age subjected to emergency appendectomy due to acute appendicitis between 1/9/2013 and 1/12/2014 were prospectively enrolled. Informed consent was obtained from all patients. Patients subjected to nonoperative management were excluded. Data collection included demographics, time of onset of abdominal pain, antibiotic administration, radiological investigations, surgical approach, post-operative complications, histology reports, hospital length of stay (HLOS), and follow-up within 30-day.

To determine time-dependent associations between delay of surgery and complications all patients were stratified into subgroups of 12-h time increments from onset of abdominal pain to surgery. Primary outcome was complications per comprehensive complication index (CCI) [7] in correlation with time from onset of the abdominal pain to appendectomy. CCI is a recently published postsurgical morbidity assessment scale based on Clavien-Dindo (CD) classification [8]. While the CD scale includes only the most severe surgical complication, the CCI includes all surgical complications in a scale ranging from 0 to 100. The CCI score of zero means no complications and a score of 100 is translated into a complication burden that results in patient's death. All complications are weighted for their severity per CCI.

Complication in this investigation was defined as any deviation from normal postoperative course with 30-day follow-up included. Secondary outcomes were duration of operation, HLOS, and incidence of complications within 30-day follow-up after hospital discharge.

Definitions of surgical site infections were based on the CDC definitions [9]. Wound infection was defined as a surgical site infection (SSI) divided into a superficial incisional SSI involving skin and subcutaneous tissue and a deep SSI involving deep soft tissues of the incision. Intra-abdominal infection was defined as an organ/space SSI involving any part of the body deeper than fascial/muscle layers.

All imaging studies and surgical interventions, laparoscopic or open appendectomy, were performed at the discretion of an attending surgeon. Blood samples including C-reactive protein (CRP) and white blood cell count (WBC) were obtained in all the patients after admission to Emergency Department. Perioperative antibiotic therapy

was administered at the discretion of treating physician. Decision for drainage was made by attending surgeon and was utilized in general peritonitis, periappendicular abscess, or when highly contaminated surgical field was encountered.

All surgical specimens were subjected to histology. Based on the histological diagnosis, patients were stratified into five subgroups using disease severity score (DSS): grade 1 (G1), inflamed; grade 2 (G2), gangrenous; grade 3 (G3), perforated with localized free fluid; grade 4 (G4), perforated with regional abscess and grade 5 (G5), perforated with diffuse peritonitis [10].

Follow-up at 30 days after discharge included complications per CD classification and CCI. All complications and readmissions within 30 days after discharge were documented.

The *P* values for categorical variables were derived from the Chi-square or 2-sided Fisher's exact test and for continuous variables the Student's *t* test or the Mann–Whitney tests were deployed. Logistic regression analysis was used to compare the CCI, complications, antimicrobial therapy, duration of surgery, conversion rate, placement of a drain, HLOS, readmission rate, and the rate of SSI between subgroups. Values are reported as mean $\pm$ standard deviation (SD) for continuous variables and as percentages for categorical variables. *P* values < 0.05 were set as statistical significance level. All analyses were performed using the Statistical Package for Social Sciences (SPSS for Mac[®]), version 16.0 (SPSS Inc., Chicago, IL).

Results

Overall, during the 15-month study period, 270 appendectomies were performed and 266 (98.5 %) of patients were included. Four patients declined to participate in the study.

Table 1 depicts demographic and clinical characteristics of the cohort. The sole significant difference in demographic profile was the mean age of the study groups that was entered into logistic regression model. The mean in-hospital time to surgery was 6.3 ± 5.7 hours and did not differ significantly between the groups.

Mean WBC on admission was $13.1 \pm 3.9 \times 10^9/L$ and mean CRP was 47.8 ± 71.9 mg/L. Overall, 88.6 % of patients were undergoing ultrasound investigation and 20.1 % computed tomography scan, respectively, before the operation.

A total of 95.1 % of patients received perioperative intravenous antibiotics at the discretion of the treating physician. Overall, 4.9 % ($n = 13$) of patients did not receive perioperative antibiotics. Two out of 13 cases (15 %) of patients not receiving perioperative antibiotics

Table 1 Demographic and clinical characteristics of all patients

Time from onset of abdominal pain to surgery	Total n = 266	0–12 h (n = 28)	13–24 h (n = 101)	25–36 h (n = 58)	37–48 h (n = 26)	>48 h (n = 53)	P
Age (years)	35.4 ± 14.8	33.1 ± 14.0	32.4 ± 14.4	36.3 ± 13.8	40.6 ± 14.8	39.0 ± 15.9	0.020
BMI	25.4 ± 4.5	24.4 ± 4.9	25.3 ± 4.6	25.9 ± 4.5	25.0 ± 5.1	25.6 ± 3.9	0.661
Male	51.1 % (136)	67.9 % (19)	49.5 % (50)	55.2 % (32)	42.3 % (11)	45.3 % (24)	0.272
Previous IA surgery	9.8 % (26)	7.1 % (2)	7.9 % (8)	8.6 % (5)	3.8 % (1)	18.9 % (10)	0.152
Perioperative AB	95.1 % (252)	100 % (27)	96.0 % (97)	96.6 % (56)	96.2 % (25)	88.7 % (47)	0.159
In-hospital delay	6.3 ± 5.7	4.6 ± 1.7	6.3 ± 3.3	5.8 ± 3.1	6.4 ± 3.0	8.0 ± 11.1	0.107
Pre-hospital delay	27.1 ± 26.9	4.9 ± 2.4	11.3 ± 4.3	22.7 ± 4.1	36.4 ± 4.3	69.7 ± 31.7	<0.001

Abbreviations: *hrs* hours, *n* number of patients, *BMI* body mass index, *IA* intra-abdominal, *AB* antibiotic

developed one superficial SSI and one intra-abdominal infection.

Surgical interventions are depicted in Table 2. Most patients were subjected to laparoscopic appendectomy at 83.1 %. Duration of operation and intraoperative placement of a drain increased significantly with longer time intervals to surgery (adj. $P < 0.001$). Three patients required conversion from laparoscopy to open midline laparotomy due to severe intra-abdominal adhesions. All the primarily performed midline laparotomies were performed due to general peritonitis.

Histology findings based on DSS are shown in Table 3. In patients with G4 and G5 acute appendicitis, the overall time interval from onset of symptoms to operation was beyond 36 hours ($P < 0.001$ for G4 and $P = 0.01$ for G5). For G1 cases, time interval was mostly <24 h ($P < 0.001$). In 1.1 % ($n = 3$) of patients histology revealed malignancy (carcinoids) and in 8.3 % non-inflamed appendix was encountered.

A detailed description of post-appendectomy complications and antibiotic therapy are presented in Table 4. The prevalence of postoperative complications and need for antimicrobial therapy correlated with extended time interval to surgery. All the patients with DSS >2 received intravenous antibiotics post-appendectomy.

Complications per CD classification did not show statistically significant correlation with prolonged time interval to surgery. However, CCI experienced a stepwise-adjusted increase in complications with delays from symptoms to surgery (adj. $P = 0.037$) (Figure 1). Overall, grade I and grade II type of CD complications predominated. A total of 7.1 % ($n = 19$) of patients developed a SSI during hospital stay (20 %) or post-discharge (80 %), respectively. Intra-abdominal infections, at 80 % ($n = 8$), were the predominant cause of all readmissions ($n = 10$) in addition to one *Clostridium difficile* colitis and one deep SSI. No mortalities occurred.

HLOS was significantly longer with increasing time to surgery and was about three-fold higher in the >48 h

subgroup compared to the <12 h subgroup. The follow-up demonstrated no significant outcome differences between the subgroups (Table 5).

Discussion

We hypothesized that delayed presentation with an extended time interval from onset of abdominal pain to surgery may increase post-appendectomy complications. The present study proved our hypothesis and demonstrated that post-appendectomy complications are associated with extended overall time interval from the very first symptoms to surgery. Also, all the advanced DSS cases (G4 and G5) were found in the subgroups of patients with appendicitis subjected to appendectomy beyond 36 h from the onset of symptoms.

Multiple previous investigations have evaluated the impact of time interval from hospital admission to surgery on outcomes in patients with acute appendicitis [11–20]. Busch et al. observed that an in-hospital delay >12 h increased considerably the risk of perforation and adverse events [11]. Also, Teixeira and colleagues in an analysis of 4529 appendectomies noted that in-hospital delay >6 h independently increased the risk of surgical site infections [12]. Likewise, in a study by Udgiri et al., an in-hospital delay to surgery beyond 10 hours significantly increased incidence of complications [13]. Nevertheless, some studies have found contrary results. In a study by Shin and co-authors, no significant difference in outcomes was noted between the subgroups waiting for operation less than 8 hours versus more than 8 hours [14]. In another large study by Drake and colleagues, no associations between in-hospital time prior to surgery and appendiceal perforations were detected [15]. Some other studies have found an in-hospital delay <24 h being a safe practice [16–19].

Our study documented prospectively the entire time segment from the onset of very first symptoms prior to hospital admission to the subsequent surgery. Very few previous studies have evaluated the total time interval from

Table 2 Duration of operation and surgical interventions of all patients

Time from onset of abdominal pain to surgery	Total (n = 266)	0–12 h (n = 28)	13–24 h (n = 101)	25–36 h (n = 58)	37–48 h (n = 26)	>48 hrs (n = 53)	P	adj. P*
Duration of OP (min)	41.2 ± 18.3	33.1 ± 11.9	36.6 ± 16.5	41.3 ± 16.8	46.4 ± 21.0	51.2 ± 20.1	<0.001	<0.001
Operations								
Open	13.9 % (37)	17.9 % (5)	9.9 % (10)	15.5 % (9)	11.5 % (3)	18.9 % (10)	0.549	0.297
Laparoscopic	83.1 % (221)	82.1 % (23)	90.1 % (91)	84.5 % (49)	76.9 % (20)	71.7 % (38)	0.056	0.019
Conversion	1.1 % (3)	0 % (0)	0 % (0)	0 % (0)	11.5 % (3)	0 % (0)	<0.001	0.273
ML	1.9 % (5)	0 % (0)	0 % (0)	0 % (0)	0 % (0)	9.4 % (5)	<0.001	0.989
Drain placement	22.2 % (59)	3.6 % (1)	7.9 % (8)	20.7 % (12)	42.3 % (11)	50.9 % (27)	<0.001	<0.001

Abbreviations: *hrs* hours, *n* number of patients, *OP* operation, *min* minutes, *Conversion* conversion from laparoscopic to midline laparotomy, *ML* midline laparotomy

*Adjusted for age

Table 3 Histology findings and distribution by disease severity score (G1–G5) of all patients

Time from onset of abdominal pain to surgery	Total (n = 266)	0–12 h (n = 28)	13–24 h (n = 101)	25–36 h (n = 58)	37–48 h (n = 26)	>48 h (n = 53)	P
Normal appendix							
G1	8.3 % (22)	14.3 % (4)	9.9 % (10)	1.7 % (1)	3.8 % (1)	11.3 % (6)	0.179
G2	59.4 % (158)	71.4 % (20)	75.2 % (76)	58.6 % (34)	46.2 % (12)	30.2 % (16)	<0.001
G3	13.9 % (37)	10.7 % (3)	11.9 % (12)	25.9 % (15)	7.7 % (2)	9.4 % (5)	0.056
G4	12.8 % (34)	3.6 % (1)	3.0 % (3)	13.8 % (8)	34.6 % (9)	24.5 % (13)	<0.001
G5	2.6 % (7)	0 % (0)	0 % (0)	0 % (0)	3.8 % (1)	11.3 % (6)	<0.001
Carcinoid	1.9 % (5)	0 % (0)	0 % (0)	0 % (0)	3.8 % (1)	7.5 % (4)	0.01
	1.1 % (3)	0 % (0)	0 % (0)	0 % (0)	0 % (0)	5.7 % (3)	0.016

Abbreviations: *hrs* hours, *n* number of patients, *G1* grade 1 (inflamed), *G2* grade 2 (gangrenous), *G3* grade 3 (perforated with localized free fluid), *G4* grade 4 (perforated with regional abscess), *G5* grade 5 (perforated with diffuse peritonitis)

Table 4 Complications overall, per Clavien-Dindo classification and comprehensive complication index of all patients

Time from onset of abdominal pain to surgery	Total (n = 266)	0–12 h (n = 28)	13–24 h (n = 101)	25–36 h (n = 58)	37–48 h (n = 26)	>48 h (n = 53)	P	Adj. P*
Post-OP AB therapy in- hosp	64.3 % (171)	64.3 % (18)	49.5 % (50)	65.5 % (38)	80.8 % (21)	83.0 % (44)	<0.001	0.002
Post-OP complications in-hosp	13.2 % (35)	3.6 % (1)	4.0 % (4)	17.2 % (10)	19.2 % (5)	28.3 % (15)	<0.001	<0.001
CD I	9.8 % (26)	14.3 % (4)	5.0 % (5)	12.1 % (7)	11.5 % (3)	13.2 % (7)	0.348	0.374
CD II	10.5 % (28)	0 % (0)	9.9 % (10)	13.8 % (8)	15.4 % (4)	11.3 % (6)	0.322	0.270
CD IIIa	1.5 % (4)	0 % (0)	0 % (0)	3.4 % (2)	3.8 % (1)	1.9 % (1)	0.347	0.254
CD IIIb	0.4 % (1)	0 % (0)	0 % (0)	0 % (0)	0 % (0)	1.9 % (1)	0.401	0.992
CD IVa	0.4 % (1)	0 % (0)	0 % (0)	0 % (0)	0 % (0)	1.9 % (1)	0.401	0.963
CD IVb	0 % (0)	0 % (0)	0 % (0)	0 % (0)	0 % (0)	0 % (0)	–	–
CD V	0 % (0)	0 % (0)	0 % (0)	0 % (0)	0 % (0)	0 % (0)	–	–
CCI	4.07 ± 9.09	1.24 ± 3.10	2.60 ± 6.76	5.35 ± 9.91	5.82 ± 10.03	6.09 ± 12.49	0.038	0.037

Abbreviations: hrs hours, n number of patients, post-OP postoperative, AB antibiotic, hosp hospital, CD Clavien-Dindo, CCI comprehensive complication index

*Adjusted for age

onset of symptoms to operation [3, 4, 21, 22]. A large retrospective study by Dittillo et al. demonstrated that the severity of histology and complication rate was time-dependent and delay of appendectomy was associated with poor outcomes. These investigators noted that the risk of advanced appendicular pathology increased 13-fold when the total time interval was greater than 71 h [21]. Two other retrospective studies analyzed the effects of delay in surgery on outcomes [4, 22]. Sadot et al. found that a total time interval beyond 48 hours significantly increased the risk for perforation [22]. Likewise, Bickell et al. observed similar results when overall interval from admission to surgery was over 36 h [4]. Similarly, a prospective study with, however, a small number of patients by Temple et al. observed that a delay in presentation accounted for most of the perforations [3]. Nevertheless, most of the studies analyzing the total time interval are limited by retrospective design [4, 21, 22] nor did these studies analyze post-operative adverse events [3, 22]. With regard to HLOS, many studies have indicated that longer interval or in-hospital delay increased considerably the post-appendectomy length of stay [13, 21].

Overall, our results are in coherence with the aforementioned studies documenting poorer outcomes with an extended time interval from admission to surgery. Most importantly, we utilized the CCI as a useful tool to evaluate post-appendectomy complications. In the present study, CCI showed stepwise significant adjusted increase in relation to the 12-h time increments from symptoms to surgery. Moreover, post-appendectomy HLOS and duration of operation showed a significant increase with prolonged time to surgery. Likewise, with an increasing time to surgery, an intraoperative drain placement was performed more frequently in the present study (adj. $P < 0.001$). However, placement of a drain is controversial and may be associated with prolonged HLOS [23].

The 30-day follow-up revealed that 5.7 % of patients developed a SSI after discharge, which is considerably high (Table 5).

The previous investigation by Garst et al. noted a DSS distribution G1 at 62.4 %, G2 at 13.0 %, G3 at 18.7 %, G4 at 4.4 %, and G5 at 1.5 % in their study cohort of 918 patients with appendicitis, which is comparable to our study. In our study, a normal appendix was found in 8.3 % of cases and a similar incidence of normal appendicular histology between 3.1 and 15.4 % has been reported in many previous series [11, 15, 16, 21]. Thus, we believe that the population of our study is representative for the general population with acute appendicitis.

Some studies have reported that spontaneous resolution of appendicitis is common and a nonoperative management may be prudent [5, 6]. However, our study showed that most of the advanced grade cases of acute appendicitis

Table 5 Hospital length of stay and 30-day follow-up of all patients

Time from onset of abdominal pain to surgery	Total (n = 266)	0–12 h (n = 28)	13–24 h (n = 101)	25–36 h (n = 58)	37–48 h (n = 26)	>48 h (n = 53)	<i>P</i>	Adj. <i>P</i> *
HLOS (h)	61.5 ± 111.6	35.6 ± 23.6	40.5 ± 27.2	60.7 ± 50.9	71.9 ± 56.1	111.0 ± 231.6	0.003	<0.001
Post-discharge SSI	5.7 % (15)	3.6 % (1)	5.0 % (5)	10.3 % (6)	7.7 % (2)	2.0 % (1)	0.401	0.957
Readmission	3.8 % (10)	0 % (0)	4.0 % (4)	5.2 % (3)	3.8 % (1)	4.1 % (2)	0.842	0.551

Abbreviations: *hrs* hours, *n* number of patients, *HLOS* hospital length of stay, *SSI* surgical site infection

*Adjusted for age

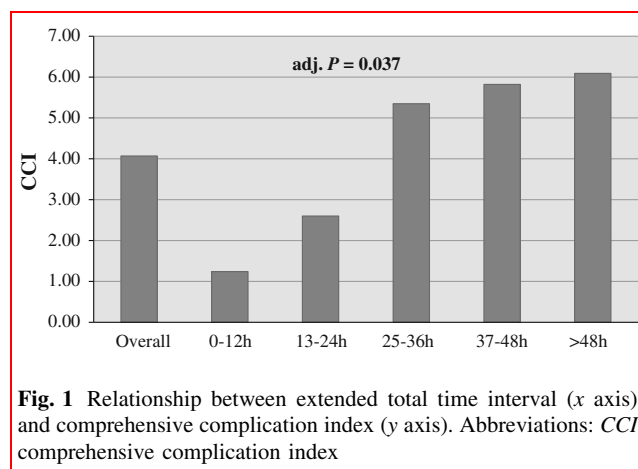


Fig. 1 Relationship between extended total time interval (*x* axis) and comprehensive complication index (*y* axis). Abbreviations: *CCI* comprehensive complication index

were in the extended time to surgery groups. Only four perforated appendicitis (G3) were observed in a less than 24 h subgroups and in all G4 and G5 cases, the time to surgery was beyond 36 hours. Therefore, we suggest that acute appendicitis may be a time-dependent process, however, more prospective studies are warranted.

The overall incidence of malignancy in appendicular specimens is reported to be about 1 % in the literature [24–26]. Likewise, we observed an incidence of malignancy in our appendicular specimens at 1.1 % (*n* = 3). Interestingly, in only one out of the three cases, the attending surgeon clinically suspected malignancy during operation. Therefore, every appendicular specimen should be sent to histology due to difficulties to differentiate benign and non-benign specimens.

Overall, 4.9 % (*n* = 13) of the cohort did not receive perioperative antibiotics and serves as a quality improvement initiative for the study site. Two patients not receiving perioperative antibiotics developed one superficial SSI and one organ/space SSI not requiring surgical intervention.

Nonoperative management of acute appendicitis with antimicrobial therapy has been evaluated in recent years with some success. However, in a recent study by Salminen et al., similar to other investigations, 27.3 % of patients

subjected to antimicrobial treatment subsequently underwent appendectomy at a follow-up within a 1-year period [27]. Also, the Cochrane meta-analysis including five prospective randomized studies of acute appendicitis subjected to surgery versus antibiotic treatment concluded that outcomes in cohorts treated with antibiotic therapy are inconclusive [28]. Therefore, our institution still considers appendectomy as the gold standard treatment for acute appendicitis.

To the best of our knowledge this is the very first prospective observational study investigating the entire time interval from initial symptoms to 30-day postoperative follow-up. Nevertheless, our study is limited by number of patients resulting in a failure to demonstrate stepwise increase in complications per CD classification among the time-stratified cohorts. Secondly, the antimicrobial therapy was administered at the discretion of treating physician introducing a potential bias in outcomes; however, a single center setting functioning per principles of a sole antibiogram counterbalances the potential bias.

Extended time interval from onset of symptoms to surgery is associated with increased duration of surgery, need of postoperative antibiotic therapy, surgical complications, and HLOS. Prompt appendectomy in acute appendicitis is warranted.

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