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ORIGINAL ARTICLE

In-hospital delay of surgery increases the rate of complicated appendicitis in patients presenting with short duration of symptoms: a retrospective cohort study

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Abstract

Purpose Current practice allows for surgery for acute appendicitis to be delayed up to 24 h in the belief that there will be no increase in complicated appendicitis rates. We evaluated the combined effect of Patient Time (between symptom onset and hospital admission) and Hospital Time (between hospital admission and surgery) on the surgical outcome. We hypothesized that in patients with a short Patient Time, increased Hospital Times will be associated with a higher rate of complicated appendicitis, even in patients operated within 24 h.

Methods Retrospective evaluation of medical files of patients operated for acute appendicitis between 12/2006 and 12/2016.

Results Of 2749 patients with acute appendicitis included in this analysis, 818 (29.8%) were admitted with symptom onset the same day as admission, 577 (21.0%) reported symptom onset had started the previous day but less than 24 h before admission, and 1354 (49.3%) had over 24 h of symptoms. In patients with symptom onset the same day, a gradual increase in the rate of complicated appendicitis was noted with increasing Hospital Times (≤6 h—6.3%; 6–12 h—9.9%; 12–18 h—14.7%; and 18–24 h—12.7%; $p=0.017$). In all other patients no differences in the rate of complicated appendicitis were noted as long as the patients were operated within 24 h of admission.

Conclusion In patients with a short Patient Time, delaying operation is associated with an increased rate of complicated appendicitis and this group of patients should be prioritized for early surgery.

Clinical Trials Study registered as ClinicalTrials.gov Identifier: NCT04689906 (https://clinicaltrials.gov/ct2/show/NCT04689906?term=ashkenazi+itamar&draw=2&rank=2).

Keywords Appendicitis · Ruptured appendicitis · Appendectomy · Timing of surgery

Introduction

For over a century, surgeons have recognized that morbidity and mortality in acute appendicitis are associated with the presence of gangrene and perforation (complicated appendicitis) [1]. Operating as early as possible became the basis of the therapeutic approach in this disease throughout the twentieth century in patients with a suspicion of acute appendicitis [2]. This aggressive approach had consequences. Many of those operated on were found to have no evidence of inflammation. A finding of normal appendixes in 20% of patients with the preoperative diagnosis of acute appendicitis "was not looked upon as an unreasonable figure, but as a necessary evil" [1].

A review of the literature reveals that the most and perhaps the only influential factor in treating appendicitis in a timely manner is the delay between symptom onset and

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presentation to the hospital (Patient Time) (see Supplemental Digital Content: SDC-1) [3–27]. Shortening the time interval between hospital admission and surgery (Hospital Time) does not seem to impact the proportion of complicated appendicitis as long as the patients are operated within 24 h following admission [22]. This has led some authors to propose that acute appendicitis is not an emergency and that delaying operation for logistical purposes is safe [23, 28].

In this study, we evaluated the combined effect of Patient Time and Hospital Time on the surgical outcome. We hypothesized that in patients with short Patient Time, increased Hospital Time will be associated with a higher rate of complicated appendicitis at the time of surgery, even in patients operated within 24 h.

Methods

Study design

This was a retrospective observational cohort study approved by the local institutional research ethics committee, in which the need for informed consent was waived (protocol 0010-13-HYMC). A similar data set was used in our previous study on the association between early imaging, surgery time, and operative findings [29]. The study was registered as ClinicalTrials.gov Identifier: NCT04689906.

Study setting and population

Included in this study were male and female patients from all ages who underwent appendectomy of acute appendicitis in a single medical center in Israel between December 1, 2006 and December 31, 2016. We evaluated all the medical records indicating an appendectomy was performed (ICD-9 codes 47.0-47.99). Patients were included if the appendectomy was performed for acute appendicitis. Patients were excluded if they underwent interval appendectomy, incidental appendectomy and appendectomy after failed antibiotic treatment for either acute appendicitis or peri-appendicular abscess. Patients with a non-inflamed appendix and those in whom symptom onset before hospitalization was not noted in their charts were also excluded.

Procedures

Information collected form the medical files included demographic data (sex and age), symptom onset (pain and/or associated symptoms), the date and time of registration to the emergency department, the date and time of surgery, the type of surgery (full laparotomy, laparoscopy, and open appendectomy through a right lower quadrant incision), and operative findings. Patient time was defined as the time interval between the onset of symptoms and the date and time the patient was registered at the emergency department, regardless of whether the patient was eventually admitted to the surgery department or to another service for an incorrect diagnosis. Hospital time was defined as the time interval between the exact time of registration in the emergency department that led to hospitalization and the exact time of onset of surgery. Some of the patients were assessed in the emergency department for abdominal pain and discharged but were subsequently readmitted and underwent appendectomy. Since the main objective of this study was to evaluate the association of increased Hospital Time with complicated appendicitis, the registration time for the readmission was considered as the onset of the Hospital Time. We considered the first encounters to be no different from any other medical encounter the patients might have had during their Patient Time before being hospitalized. Patient Time was divided into three groups: symptom onset the same day as hospitalization; symptom onset the previous day but less than 24 h; and symptom onset over 24 h prior to presentation. Patients presenting to the hospital between midnight and 8:00AM with symptom onset the evening of the previous day were counted as having symptom onset the same day. Patients who were admitted at 08:01 and whose symptoms started on the evening of the previous day were counted as having symptom onset the previous day but less than 24 h. Patient Time was further stratified for those with symptom onset over 24 h prior to presentation: 1–2 days; 2–3 days; 3–4 days, 4 days and over, and unspecified if the exact numbers of days was not noted. Hospital Time was divided into five groups according to the time interval between admission to the hospital and surgery: up to six hours (≤ 6 h), beyond six hours up to twelve hours (6–12 h), beyond twelve hours up to eighteen hours (12–18 h), beyond 18 h and up to 24 h (18–24 h) and beyond twenty-four hours (>24 h). Operative findings were classified as either non-complicated appendicitis or complicated appendicitis. If the operative finding was questionable, the pathology report was reevaluated by the authors with the pathologists. Complicated appendicitis was defined as gangrene without perforation, perforation with abscess formation or free perforation with localized or generalized peritonitis.

Sample size calculation

In this retrospective study all patients operated for acute appendicitis were included. Prior data indicated that the ratio between those with symptom onset the same day as hospitalization and those with a longer interval of symptoms would be approximately 1:2. Prior data also indicated that the failure rate (complicated appendicitis) was approximately 0.25. To identify a >0.50 difference in the rate of complicated appendicitis with an 80% power,

we calculated we will need to study at least 119 subjects with symptom onset the same day as hospitalization and 238 subjects with longer interval of symptoms. The Type I error probability associated with this test of this null hypothesis is 0.05.

Data analysis

Age, sex, Patient Time and Hospital Time were analyzed using descriptive statistics. Differences in the rate of complicated appendicitis between the groups were analyzed by either Chi-square for trend or Fisher exact probability test. All evaluations were 2-sided. The combined effect of Hospital Time as a continuous data, age, sex, and need for CT were investigated using logistic regression. Results were presented as odds ratio and 95% confidence intervals (95% CI). Data were analyzed using dedicated statistical software programs (GraphPad Prism 6.00 version for Windows, GraphPad Software Inc., San Diego, CA, IBM Corp. Released 2021. IBM SPSS Statistics for Windows, Version 28.0. Armonk, NY: IBM Corp). *P* values less than 0.05 were considered significant. Percentages were approximated to the nearest decimal and odds ratio, 95% CI and *P* values to the nearest thousandth. The work is been reported in line with the STROBE criteria.

Results

Study population

Following the identification of patients undergoing an appendectomy, 2749 patients with known timing of symptom onset who underwent appendectomy for acute appendicitis were included in this study (Fig. 1). Sixty-nine patients were excluded because the timing of symptom onset was not noted in their charts. These represent 2.4% of 2818 patients with acute appendicitis undergoing surgery. In 167 other patients, the medical files indicated that symptoms had started several days before admission to the emergency department. However, the exact number of days was not specified. These patients were included in the analysis together with other patients with symptom onset over 24 h before their presentation to the hospital.

Demographic and clinical data are presented in Table 1. Overall, 28.0% (770/2749) had an operative finding of complicated appendicitis. There were more open appendectomies at the beginning of the study but by the end almost all surgical procedures began as laparoscopic operations; this, however, is not relevant to the timing of surgery and the pathological findings.

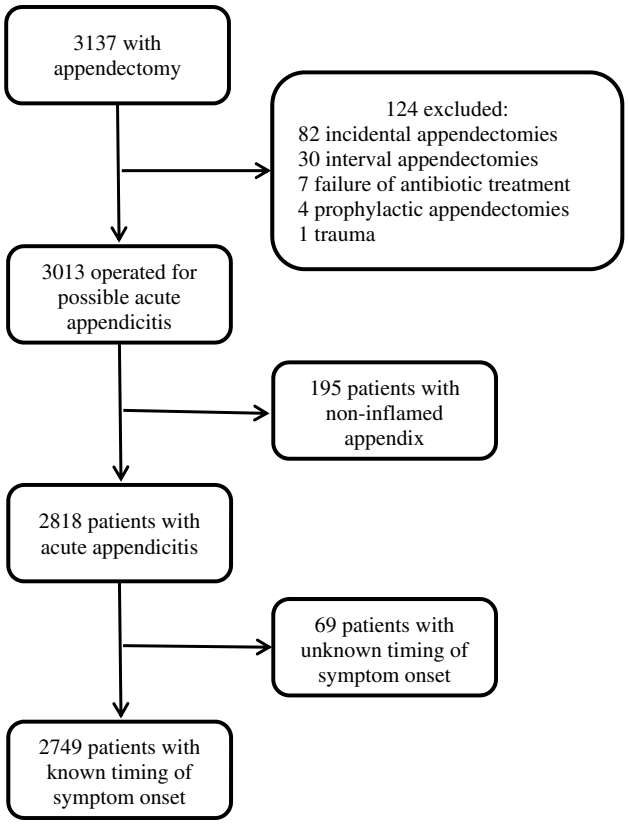

Fig. 1 Patient schema

Effect of Patient Time and Hospital Time on complicated appendicitis

Table 2 presents the association between the operative finding of complicated appendicitis and Patient Time. While only 12.7% (104/818) of those presenting the same day of symptom onset had a surgical finding of complicated appendicitis, this increased to 58.0% (101/174) in those presenting with Patient Time of 4 days or more ($p < 0.001$). Table 3 presents the association between the operative finding of complicated appendicitis and Hospital Time. In patients operated beyond 24 h, there was an increased rate of complicated appendicitis of 43.4% (112/258) ($p < 0.001$). However, no significant differences were noted between the subgroups of patients operated within 24 h ($p = 0.294$).

The combined effect of Patient Time and Hospital Time on complicated appendicitis

An evaluation of the combined effect of Patient Time and Hospital Time on the percentage of patients with complicated appendicitis is shown in Table 4. In patients admitted the same day as symptom onset, the prevalence of patients with complicated appendicitis was 6.3% (12/189) in patients operated within 6 h. This increased to 9.9% (30/303) in patients

Table 1 Patient data in 2749 patients included in the study

	Patients (%)
Age* (median 22; interquartile range 13, 36; range 0.5–92)	2749 (100)
Sex	
Male	1741 (63.3)
Female	1008 (36.7)
Patient Time (all)	
Same day	818 (29.8)
Previous day but less than 24 h	577 (21.0)
Over 24 h	1354 (49.3)
Patient Time (1354 patients admitted over 24 h)	
1–2 days	444 (16.2)
2–3 days	344 (12.5)
3–4 days	225 (8.2)
Over 4 days	174 (6.3)
Unspecified	167 (6.1)
Hospital Time	
Within 6 h	572 (20.8)
6–12 h	1278 (46.5)
12–18 h	436 (15.9)
18–24 h	205 (7.5)
Over 24 h	258 (9.4)
Type of surgery	
Open (right lower quadrant incision)	1717 (62.5)
Laparoscopy	998 (36.3)
Laparotomy	34 (1.2)
Surgical finding (overall)	
Non-complicated appendicitis	1979 (72.0)
Complicated appendicitis	770 (28.0)

*Missing data on three foreign workers

Table 2 Operative findings as a function of symptom onset before hospitalization (Patient Time)

Patient Time (days)	Operative findings		*P* value*
	Non-complicated appendicitis (%)	Complicated appendicitis (%)	
Same day	714 (87.3)	104 (12.7)	< 0.001
Previous day but less than 24 h	455 (78.9)	122 (21.1)	
1–2	323 (72.7)	121 (27.3)	
2–3	204 (59.3)	140 (40.7)	
3–4	107 (47.6)	118 (52.4)	
> 4	73 (42.0)	101 (58.0)	
**Unspecified	103	64	

*To allow chi-square for trend, calculation data from same day were combined with data from previous day but less than 24 h

**Patient Time more than 24 h but not otherwise specified

operated within 6–12 h from admission and 14.7% (24/163) in patients operated within 12–18 h ($p = 0.017$ for patients operated within 24 h from admission). With longer Patient Time (if symptom onset occurred the previous day but less than 24 h prior to presentation, or in patients with symptom onset over 24 h prior to presentation), shorter Hospital Time did not result in decreased prevalence of complicated appendicitis.

When Hospital Time in those with same day symptom onset was analyzed together with other possible covariates such as age, sex, and the need for CT, Hospital Time remained associated with complicated appendicitis (odds ratio 1.114, 95% CI 1.018–1.219; $p = 0.019$). Age, sex, and the need for CT were not associated with complicated appendicitis. Evaluation of possible interactions shows that the association of Hospital Time and complicated appendicitis partly relied on age (odds ratio 0.996, 95% CI 0.992–1.000; $p = 0.38$).

Subanalysis in young and elderly patients

A separate analysis of 178 patients up to 12 years of age with symptom onset the same day as hospitalization revealed that there was still a significant increase in complicated appendicitis when surgery was delayed beyond 12 h (see Supplementary Digital Content: SDC-2). The complicated appendicitis rates for these young patients operated within 0–6 h' were 9.8% (6/61); 6–12 h'—9.1% (6/66); 12–18 h'—31.0% (9/29); and 18–24 h'—22.2% (2/9) ($p = 0.021$). There were 25 patients aged 65 or older with symptom onset the same day, a number too small to allow meaningful statistical analysis (see Supplementary Digital Content: SDC-2). Of note, Patient Time of one day or more was more common in this age group compared to younger patients (62.9% vs. 48.7%; $p = 0.008$).

Subanalysis of perforated appendicitis

The association of short Patient Time and the surgical finding of perforated appendicitis was also evaluated. Three hundred and fifty (12.7%) had a surgical finding of localized or extensive perforation (see Supplementary Digital Content: SDC-2). Of these, 37 presented with symptom onset the same day as hospitalization. The perforated appendicitis rates in patients presenting with symptom onset the same day as hospitalization and operated within 0–6 h′ were 1.1% (2/189); 6–12 h′—4.6% (14/303); 12–18 h′—6.1% (10/163); and 18–24 h′—1.4% (1/71) (p = 0.227).

Discussion

In the current study we evaluated the effect of time from registration at the hospital's emergency department until surgery on the rate of complicated appendicitis for patients with

Table 3 Operative findings as a function of timing of surgery from admission (Hospital Time)

Hospital Time (hours)	Operative findings		*P* value for patients with Hospital Time up to 24 h
	Non-complicated appendicitis (%)	Complicated appendicitis (%)	
≤6	438 (76.6)	134 (23.4)	0.294
6–12	925 (72.4)	353 (27.6)	
12–18	320 (73.4)	116 (26.6)	
18–24	150 (73.2)	55 (26.8)	
>24	146 (56.6)	112 (43.4)	

Table 4 The combined effect of symptom onset before hospitalization (Patient Time) and timing from admission to surgery (Hospital Time) on operative findings

Patient Time	Hospital Time (hours)	Operative findings		*P* value for patients operated within 24 h from admission
		Non-complicated appendicitis (%)	Complicated appendicitis (%)	
Same day	≤6	177 (93.7)	12 (6.3)	0.017
	6–12	273 (90.1)	30 (9.9)	
	12–18	139 (85.3)	24 (14.7)	
	18–24	62 (87.3)	9 (12.7)	
	>24	63 (68.5)	29 (31.5)	
Previous day but less than 24 h	≤6	61 (79.2)	16 (20.8)	0.150
	6–12	273 (82.2)	59 (17.8)	
	12–18	80 (76.2)	25 (23.8)	
	18–24	20 (69.0)	9 (31.0)	
	>24	21(61.8)	13 (38.2)	
>24 h	≤6	200 (65.4)	106 (34.6)	0.627
	6–12	379 (58.9)	264 (41.1)	
	12–18	101 (60.1)	67 (39.9)	
	18–24	68 (64.8)	37 (35.2)	
	>24	62 (47.0)	70 (53.0)	

P value—Chi square for trend

varying duration of symptoms before admission, irrespective of the reasons for delay. Our results suggest that patients with acute appendicitis who present with symptom onset the same day as their admission to the emergency department have a significantly higher rate of complicated appendicitis if their surgery is delayed beyond 6 h.

Many studies have been done to quantify the influence of time on the surgical finding of complicated appendicitis (SDC-1) [3–27]. The vast majority of these support the widespread concept that the main contributor to the development of complicated appendicitis is Patient Time. These studies also show that increased Hospital Time up to 24 h does not increase the prevalence of complicated appendicitis [27]. However, none of the studies published to date has evaluated the combined effect of Patient Time and Hospital Time upon the surgical finding of complicated appendicitis.

It should be noted that all the studies were retrospective and the accuracy of timing of symptom onset before admission may be called into question. In this study we chose a strict definition for patients presenting with "same day" symptoms allowing us to evaluate the combined association of a subset of patients with short Patient Time and different Hospital Time upon complicated appendicitis.

There may be several reasons for the greater contribution of Patient Time to the rate of complicated appendicitis compared with Hospital Time. Patient Time in most studies is longer than Hospital Time. In most studies, Patient Time is commonly longer than 24 h. In this study, almost half of the patients presented to the emergency department beyond 24 h from symptom onset. If Patient Time is prolonged, Hospital Time may have less effect on the incidence of complicated appendicitis. Furthermore, Hospital Time is measured in hours, whereas Patient time is measured in days. In most studies, the time periods differentiating between Hospital Time subgroups were only 6 h long. Differences in the proportion of complicated appendicitis

between different subgroups will be more pronounced if the time range defining them is longer. It is not surprising, therefore, that the differences in the frequency of complicated appendicitis are relatively small and underpowered to reveal significance between the different subgroups of Hospital Time. Consequently, only when patients operated within 24 h are compared with those operated beyond 24 h could a difference be established in these studies [12, 22].

In this study, when all patients were analyzed together, irrespective of Patient Time, the rate of patients with complicated appendicitis was in the range of 23.4–27.6% in patients operated within 24 h. The rate of complicated appendicitis rose to beyond 40% only if surgery was delayed beyond 24 h. Similar to the UK National Surgical Research Collaborative and the meta-analysis performed by van Dijk et al., the rate of complicated appendicitis in this study did not differ between patients operated within 6 h, 6–12 h, 12–18 h, and 18–24 h [22, 27]. The most extensive study evaluating Hospital Time is that of Ingraham et al., who analyzed 32,782 patients operated for acute appendicitis between 2005 and 2008 and were registered in the American College of Surgeons National Surgical Quality Improvement Program [12]. Patients who were operated within 6 h of admission were compared to patients who were operated between 6 and 12 h from admission, and to patients operated beyond 12 h from admission. These represented 75.2%, 15.1%, and 9.8% of the patients respectively. No differences were found between the groups for the overall incidence of complications, and the incidence of severe complications and/or mortality. The author of an editorial accompanying this study commented that it is now clear that there is no excess incidence of complications in those operated beyond 12 h compared to those operated as soon as possible [28]. He further suggested that there is no reason to operate for acute appendicitis at nighttime. Patients with acute appendicitis should be have their appendectomy "as soon as is convenient" rather than as soon as possible.

The findings of this study, which takes into account not only Hospital Time but also Patient Time, question this recommendation. Once the patients presenting to the emergency department the same day as symptom onset were stratified according to Hospital Time, differences in the rates of complicated appendicitis observed beyond 6 h were not only statistically significant but also clinically important. It is not uncommon that in patients presenting to the ED in the late evening of the day that their symptoms began, surgery is postponed to the morning after. This surgery may also commonly be listed at the end of the elective schedule, delaying the surgery even further. However, in these patients with a short Patient Time, delay of surgery for any reason will be associated with higher rates of complicated appendicitis.

Limitations

As with all the other studies that have been published about this topic, this was a retrospective study and the exact time of onset of symptoms could not always be determined. Physicians recording the patients' history commonly used broad terms when describing symptom onset such as the "day before", "yesterday afternoon", and others. We chose a strict definition to define those with symptom onset the same day. This limits the conclusions of this study to 818 patients (29.8%) within this cohort of 2749 patients.

For this study, we differentiated between complicated and non-complicated appendicitis. We mainly relied on the clinical assessment made during surgery rather than the final pathological reports, which did not always elaborate on gangrenous changes or perforation, even when these were clinically apparent. Pathology reports were consulted in all those cases in which the diagnosis of appendicitis was questionable. The presence of gangrene relies not only on microscopy but also on gross features such as a friable appendiceal wall and purple, green, or black discoloration [30]. Even if perforation is clinically apparent, demonstrating pathologically the perforation site may be difficult, if not impossible [30]. Complicated appendicitis includes different pathologies with different risks for developing adverse outcomes. These pathologies range from gangrene, including tip gangrene, to minor and major perforations. Data provided in this study reveal non-significant differences in the rate of perforation between patients operated within 6 h to those operated beyond 6 h. Though this cohort is large, the low rate of perforations is not powered to reveal significance between these two groups of patients. This does not, however, diminish the clinical importance of a finding of gangrene without perforation: Unlike patients with non-complicated appendicitis, in patients with surgical findings of gangrene, whether limited to the tip or the entire appendix, antibiotic treatment is commonly extended beyond the prophylactic dose. Extending antibiotic treatment beyond the prophylactic dose may be associated with longer hospital stay and other risks, such as increased risk of *Clostridium difficile* infection [31].

In this study we analyzed all patients operated on for acute appendicitis regardless of their age. A subgroup analysis showed that increasing Hospital Time in children was also associated with an increase in complicated appendicitis. Only 25 elderly patients with same-day symptoms were available for analysis, none of whom was operated within 6 h. Similar to the analysis of the subgroup of patients with perforated appendix, analysis of relatively small subgroups should rely on larger cohorts. All patients operated within 10 years at a single institution were included in this study. Increasing the size of subgroups considerably would require a multicenter effort.

Apart from age, we did not evaluate possible covariates that might influence the rate of complicated appendicitis such as diabetes mellitus. Still, we and others evaluating the association of complicated appendicitis with either extremes of age or diabetes mellitus suggest that these are associated with a significantly longer time from symptom onset to diagnosis and late referral [32].

We did not collect data on whether the patients presented with clinical or laboratory signs of sepsis. We should assume that patients presenting with sepsis underwent surgery as soon as possible rather than late. This would result in a higher proportion of complicated appendicitis in the subgroup of patients operated on early. Removing these patients from the analysis would further decrease the rate of complicated appendicitis in those operated within 6 h in all Patient Time subgroups.

The reasons for delaying surgery beyond six and twelve hours were not recorded. We assume that operating room availability and postponement of operations up until the morning hours or up until the end of the elective schedule might have been significant factors in most patients.

Conclusion

There may be a myriad of reasons to delay appendectomy, but our results show that in patients who present early following their symptom onset, the rate of complicated appendicitis will more than double if surgery is delayed beyond 12 h. These results suggest that for patients presenting early in their disease, surgery for acute appendicitis cannot be delayed safely as has come to be accepted over the past decade.

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Data availability Patient data included in this research has not been placed in a data sharing repository. According to the research ethics committee protocol, the patient data is to be kept deidentified and under password. Data can be made available for monitoring purposes by an official body if requested.

Code availability None to declare.

Declarations

Conflict of interest There are no conflicts of interest to declare concerning the content of this article. Each authors submitted a COI disclosure form.

Ethical approval The study was performed in accordance with the ethical standards as laid down in the 1964 Declration of Helsinki and its ammendments. The appropriate passage is included in the methods section.

Consent to participate This was a retrospective observational cohort study approved by the local institutional research ethics committee, in which the need for informed consent was waived (protocol 0010-13-HYMC).

Consent for publication This manuscript does not include materials published under copyright. Nor does this manuscript include images that may identify patients in need of consent.

References

1. Cantrell JR, Staffor ES. The diminishing mortality from appendicitis. Ann Surg. 1955;141(6):749–56. https://doi.org/10.1097/00000658-195506000-00001.
2. Temple CL, Huchcroft SA, Temple WJ. The natural history of appendicitis in adults: a prospective study. Ann Surg. 1995;221(3):278–81. https://doi.org/10.1097/00000658-199503000-00010.
3. Abou-Nukta F, Bakhos C, Arroyo K, Koo Y, Martin J, Reinhold R, Ciardiello K. Effects of delaying appendectomy for acute appendicitis for 12 to 24 hours. Arch Surg. 2006;141(5):504–7. https://doi.org/10.1001/archsurg.141.5.504.
4. Bickell NA, Aufses AH, Rojas M, Bodian C. How time affects the risk of rupture in appendicitis. J Am Coll Surg. 2006;202(3):401–6. https://doi.org/10.1016/j.jamcollsurg.2005.11.016.
5. Busch M, Gutzwiller FS, Aellig S, Kuettel R, Metzger U, Zingg U. In-hospital delay increases the risk of perforation in adults with appendicitis. World J Surg. 2011;35(7):1626–33. https://doi.org/10.1007/s00268-011-1101-z.
6. Ditillo MF, Dziura JD, Rabinovici R. Is it safe to delay appendectomy in adults with acute appendicitis? Ann Surg. 2006;244(5):656–60. https://doi.org/10.1097/01.sla.0000231726.53487.dd.
7. Drake FT, Mottey NE, Farrokhi ET, Florence MG, Johnson MG, Mock C, Steel SR, Thirlby RC, Flum DR. Time to appendectomy and risk of perforation in acute appendicitis. JAMA Surg. 2014;149(8):837–44. https://doi.org/10.1001/jamasurg.2014.77.
8. Eko FN, Ryb GE, Drager L, Goldwater E, Wu JJ, Counihan TC. Ideal timing of surgery for acute uncomplicated appendicitis. North Am J Med Sci. 2013;5(1):22–7. https://doi.org/10.4103/1947-2714.106186.
9. Eldar S, Nash E, Sabo E, Matter I, Kunin J, Mogilner JG, Abrahamson J. Delay in surgery in acute appendicitis. Am J Surg. 1997;173(3):194–8. https://doi.org/10.1016/s0002-9610(96)00011-6.
10. Giraudo G, Baracchi F, Pellegrino L, Dal Corso HM, Borghi F. Prompt or delayed appendectomy? Influence of timing of surgery for acute appendicitis. Surg Today. 2013;43(4):392–6. https://doi.org/10.1007/s00595-012-0250-5.
11. Hansson LE, Laurell H, Gunnarsson U. Impact of time in the development of acute appendicitis. Dig Surg. 2008;25(5):394–9. https://doi.org/10.1159/000180451.

12. Ingraham AM, Cohen ME, Bilimoria KY, Ko CY, Hall BL, Russell TR, Nathens AB. Effect of delay to operation on outcomes in adults with acute appendicitis. Arch Surg. 2010;145(9):886–92. https://doi.org/10.1001/archsurg.2010.184.
13. Jeon BG, Kim HG, Jung KH, Lim HI, Kim SW, Park JS, Kim KH, Kim ID. Appendectomy: should it be performed so quickly? Am Surg. 2016;82(1):65–74 (**PMID: 26802860**).
14. Kearney D, Cahill RA, O'Brien E, Kirwan WO, Redmond HP. Influence of delys on perforation risk in adults with acute appendicitis. Dis Colon Rectum. 2008;51(12):1823–7. https://doi.org/10.1007/s10350-008-9373-6.
15. Lee SL, Ho HS. Acute appenidicitis: Is there a difference between children and adults? Am Surg. 2006;72(5):409–13 (**PMID: 16719195**).
16. Maroju NK, Robinson Smile S, Sistla SC, Narishman R, Sahai A. Delay in surgery for acute appendicitis. Anz J Surg. 2004;74(9):773–6. https://doi.org/10.1111/j.1445-1433.2004.02785.x.
17. Omundsen M, Dennett E. Delay in appendicectomy and associated morbidity: a retrospective review. ANZ J Surg. 2006;76(3):153–5. https://doi.org/10.1111/j.1445-2197.2006.03673.x.
18. Sadot E, Wasserberg N, Shapiro R, Keidar A, Oberman B, Sadetzki S. Acute appendicitis in the twenty-first century: should we modify the management protocol? J Gastrointest Surg. 2013;17(8):1462–70. https://doi.org/10.1007/s11605-013-2232-3.
19. Schnuriger B, Laue J, Kroll D, Inderbitzin D, Seiler CA, Candinas D. Introduction of a new policy of no nighttime appendectomies: impact on appedinceal perforation rates and postoperative morbidity. World J Surg. 2013;38(1):18–24. https://doi.org/10.1007/s00268-013-2225-0.
20. Taylor M, Emil S, Nguyen N, Ndiforchu F. Emergent vs. urgent appendectomy in children: a study of outcomes. J Ped Surg. 2005;40(12):1912–5. https://doi.org/10.1016/j.jpedsurg.2005.08.005.
21. Teixeira PG, Sivrikoz E, Inaba K, Talving P, Lam L, Demetriades D. Appendectomy timing. Waiting until the next morning increases the risk of surgical site infections. Ann Surg. 2012;256(3):538–43. https://doi.org/10.1097/SLA.0b013e318265ea13.
22. The United Kingdom National Surgical Research Collaborative. Safety of sort, in-hospital delays before surgery for acute appendicitis: multicentre cohort study, systematic review, and meta-analysis. Ann Surg. 2014;259(5):894–903. https://doi.org/10.1097/SLA.0000000000000492.
23. Yardeni D, Hirschl RB, Drongowski RA, Teitelbaum DH, Geiger JD, Coran AG. Delayed versus immediate surgery in acute appendicitis: do we need to operate during the night? J Pediatr Surg. 2004;39(3):464–9. https://doi.org/10.1016/j.jpedsurg.2003.11.020.
24. Nagpal K, Udgiri N, Sharma N, Curras E, Cosgrove JM, Farkas DT. Delaying an appendectomy: is it safe? Am Surg. 2012;78(8):897–900 (**PMID: 22856499**).
25. Udgiri N, Curras E, Kella VK, Nagpal K, Cosgrove J. Appendicitis, is it an emergency? Am Surg. 2011;77(7):898–901 (**PMID: 21944355**).
26. Elniel M, Grainger J, Nevins EJ, Misra N, Skaife P. 72 h is the time critical point to operate acute appendicitis. J Gastrointest Surg. 2018;22(2):310–5. https://doi.org/10.1007/s11605-017-3614-8.
27. van Dijk ST, van Dijk AH, Dijkgraaf MG, Boermeester MA. Meta-analysis of in-hospital delay before surgery as a risk factor for complications in patients with acute appendicitis. Br J Surg. 2018;105(8):933–45. https://doi.org/10.1002/bjs.10873.
28. Hunter JG. Letting weary surgeons sleep and saving money. Arch Surg. 2010;145(9):892. https://doi.org/10.1001/archsurg.2010.176.
29. Ashkenazi I, Zeina AR, Olsha O. Early ultrasound in acute appendicitis avoids CT in most patients but delays surgery and increases complicated appendicitis if nondiagnostic—a retrospective study. Am J Surg. 2020;219(4):683–9. https://doi.org/10.1016/j.amjsurg.2019.05.013.
30. Carr NJ. The pathology of acute appendicitis. Ann Diagn Pathol. 2000;4(1):46–58. https://doi.org/10.1016/s1092-9134(00)90011-x.
31. Hensgens MP, Goorhuis A, Dekkers OM, Kuijper EJ. Time interval of increased risk for *Clostridium difficile* infection after exposure to antibiotics. J Antimicrob Chemother. 2012;67:742–8. https://doi.org/10.1093/jac/dkr508.
32. Tsai SH, Hsu CW, Chen SC, Lin YY, Chu SJ. Complicated acute appendicitis in diabetic patients. Am J Surg. 2008;196(1):34–9. https://doi.org/10.1016/j.amjsurg.2007.05.042.