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ORIGINAL ARTICLE

72 h Is the Time Critical Point to Operate in Acute Appendicitis

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Abstract

Background and Aims Delay of operative management of acute appendicitis may adversely affect post-operative outcomes and increase the likelihood of post-operative complications occurring. We aim to correlate the duration of symptoms with intra-operative findings to create a timeline of the pathological change in appendicitis.

Methods Appendicectomies performed at a large teaching hospital between June 2015 and July 2016 were prospectively analysed. Time of onset of pain, operative findings, pre-operative C-reactive protein (CRP) and white cell count (WCC) were recorded. Intra-operative findings were categorised by the macroscopic appearance of the appendix, which was subdivided into erythematous, purulent, necrotic and perforated. These results were correlated with the symptom duration. Statistical analysis was completed using Mann-Whitney *U* and Chi-squared tests.

Results One hundred and ninety patients had histologically confirmed appendicitis during the study period. Median time to operation from symptom onset was 49 h. Median time for the appearances of erythematous, purulent, necrotic and perforated appendicitis to develop was 36.5, 41, 55.5 and 86 h, respectively (p value < 0.0001). Median CRP of the non-perforated and perforated appendicitis groups was 22 and 161 mg/L, respectively (p value < 0.0001). Our data demonstrated that after 72 h of symptoms, the likelihood of a perforated appendicitis increased significantly (p value < 0.0001) when compared to 60–72 h.

Conclusions A significant increase in the likelihood of a perforated appendicitis occurs after 72 h of symptoms, when compared to 60–72 h. We can therefore argue that it may be reasonable to prioritise patients approaching 72 h of symptoms for operative management.

Keywords Appendicitis · Acute appendicitis · Colorectal surgery · Emergency surgery · Medicolegal · Laparoscopy · Pathology · CEPOD · Perforation · Time critical

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Introduction

Appendicitis is one of the commonest general surgical emergencies worldwide.[1] In the UK alone, 35,902 cases of acute appendicitis requiring admission were recorded between March 2015 and 2016.[2] Accordingly, the appendicectomy is one of the most frequent emergency surgical operations performed with the lifetime risk of appendicectomy in males and females being 12 and 23%, respectively.[3]

Since Reginald Fitz first described the course and management of appendicitis in 1886,[4] the surgical dogma of emergent appendicectomy to prevent complications of appendicitis has

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remained until recently. Some studies now suggest that appendicitis may be treated as 'urgent' or in an ambulatory manner as opposed to as an emergency[5,6] with some authors suggesting that a select group of patients may be treated conservatively without the need for an operation.[5,7]

There is much data regarding the effect of in-hospital delays on outcomes in appendicitis.[8] However, there are few prospective studies relating time as a function to the progression of disease in appendicitis.[9] It is therefore unclear as to when it becomes time critical to operate on appendicitis based on the timeline of the history of symptoms, and which patients can have their surgery safely delayed until the following morning if the need arose.

We seek to demonstrate how the duration of symptoms can affect appendix morphology in appendicitis and at what point the risk of perforation increases significantly.

Perforated appendicitis can lead to peritonitis, sepsis and other long-term adverse effects.[10] We therefore believe this study may be of benefit to the emergency general surgeon in prioritising the operative management of appendicitis and in reducing the potential for post-operative complications. In addition, our study is unique in that it examines at both pre- and in-hospital delays as a single homogenous factor in delay which may be more applicable to actual clinical practice as opposed to solely looking at in-hospital delays.

Methods

A prospective study of appendicectomies performed at University Hospital Aintree, Merseyside, between June 2015 and July 2016 was undertaken. The operating surgeon collected the required data at the time of operation. Patients were later excluded if they did not have a histologically confirmed acute appendicitis. The operative surgeon was required to record the patient's time of onset of pain and the operative findings as well as pre-operative C-reactive protein (CRP) and white cell count (WCC). Intra-operative findings were categorised by degree of peritoneal soiling and macroscopic appearance of the appendix. The appearance of the appendix was subdivided into normal, erythematous, purulent, necrotic and perforated. For clarification, the term 'perforation' refers to macroscopic perforation with abscess and peritonitis.

Patients with perforated appendicitis were compared to patients without perforated appendicitis; these groups were compared using Mann-Whitney *U*, the five macroscopic groups were also compared using Kruskal-Wallis where appropriate. Statistical analysis was performed using Prism® version 6.0 (GraphPad Software, San Diego, California, USA). Results were considered statistically significant if $p < 0.05$.

It should be noted that in our institution the work-up for patients with suspected acute appendicitis consists of clinical evaluation and laboratory studies for WCC and CRP. In the UK, the diagnosis of appendicitis is still seen as a clinical diagnosis; it is fair to argue that the NHS does not have the resources to routinely use computed tomographic imaging for every patient presenting with right iliac fossa pain. Computed tomographic imaging is normally reserved for patients where there may be a suspicion of inflammatory bowel disease or of cancer. Pelvic ultrasound is also used by female patients of child-bearing age where there may be a suspicion of a gynaecological diagnosis.

Results

One hundred and ninety patients had histologically confirmed appendicitis; 93 (49%) were male. The median age was 34 (range 16–87) (IQR 25–49). The median time from onset of symptoms to presentation was 49 h (range 12–370 h) (IQR 32–84.75). One hundred and eighty-six (98%) had a recorded WCC available, with a median value of 13.85×10^9/L, (range $12–37 \times 10^9$/L) (IQR 10.8–17.075). One hundred and eighty-six (98%) patients had an admission CRP recorded. The median CRP was 33 (ranged < 1–546) (IQR 6–41.75).

Operative appearance demonstrated 4 macroscopically normal (group 0, 22%), 50 erythematous (group 1, 26%), 56 inflamed (group 2, 29%), 26 necrotic (group 3, 14%) and 54 perforated appendices (group 4, 28%). From here on, these groups will be referred to as group 0, 1, 2, 3 and 4, respectively.

Patients with perforated appendicitis had a higher median CRP than those without perforation which was statistically significant (22 vs 161, $p < 0.0001$) (Fig. 1a).

Patients with perforated appendicitis had a higher median WCC than those with non-perforated appendicitis, which was also statistically significant (13.1 vs 15.3, $p < 0.0092$) (Fig. 1b).

Comparison of patients with perforated appendicitis versus non-perforated appendicitis also demonstrated that the median symptom time was longer in the first group (86 vs 42 h, $p < 0.0001$) (Fig. 1c), which was statistically significant. Interestingly, all patients with > 193 h of symptoms had perforated appendicitis.

Comparison across the five subgroups demonstrated that median CRP and WCC rose across all groups ($p < 0.0001$ and $p = 0.0008$, respectively) (Fig. 2a, b). As the duration of symptoms increased, the macroscopic appearance of the appendix became worse ($p < 0.0001$) (Fig. 2c). Once patients had waited longer than 72 h after the onset of pain, there is an increased risk of perforation which is statistically significant (Fig. 3) ($p < 0.0001$).

It should be noted that there is no significant difference between < 24, 24–48 and 48–72 h regarding chances of perforation. However, between 48–72 and 72–96 h, this difference is significant ($p = 0.0011$). There is again no difference between 72–96 and > 120 h; this is demonstrated in Dunn's multiple comparison table (Table 1).

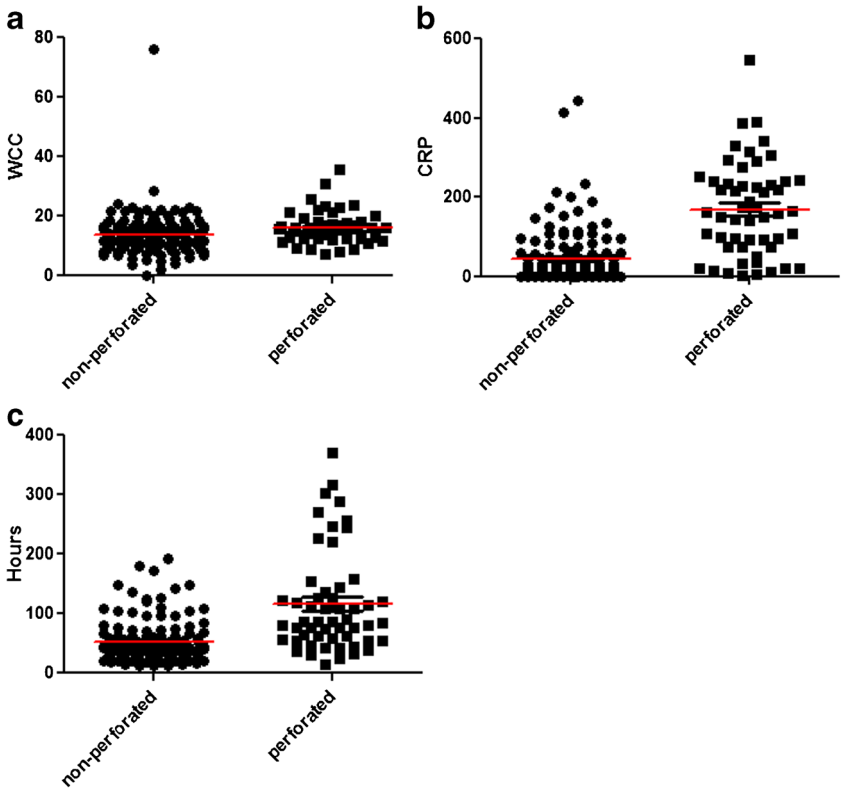

Fig. 1 Comparison of **a** WCC, **b** CRP and **c** length of time of symptoms in the perforated and non-perforated groups

Of interest, we found 18 patients had a macroscopic perforation with less than 72 h of symptoms compared to 111 patients who had non-perforated appendicitis with less than 72 h of symptoms. On comparing these two groups, we found the median CRP and WCC to be statistically significantly higher in the perforated group. On examining patients with symptoms over 72 h and no perforation and comparing those with a perforation and symptoms over 72 h, we found those with a perforation to have a higher median CRP and WCC. However, only the CRP was found to be of statistical significance when comparing these two groups. This is outlined in Table 2.

Table 3 outlines the utility of pre-operative imaging in the cohort of patients studied. CT was most commonly used pre-operatively in patients in group 4 and least commonly used in group 0 patients.

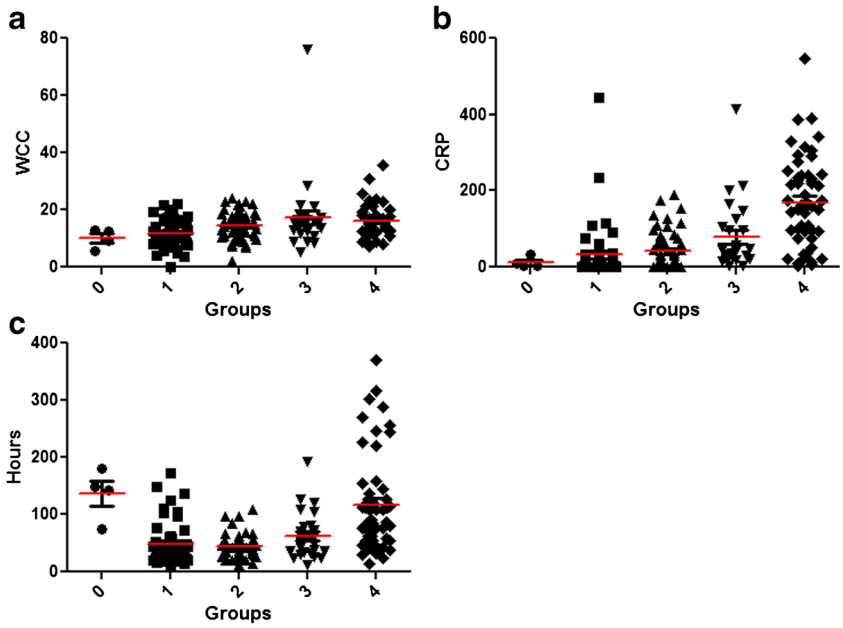

Fig. 2 Comparison of **a** WCC, **b** CRP and **c** length of time of symptoms amongst the five macroscopic appearance subgroups

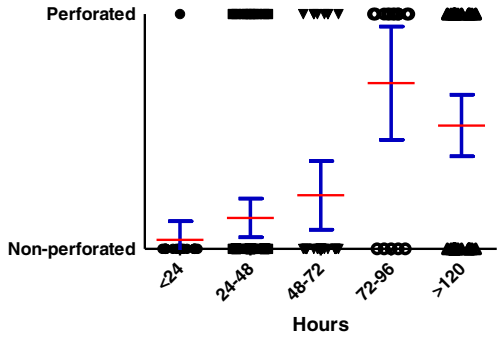

Fig. 3 Comparison of perforated and non-perforated appendicitis with increasing length of time of symptoms. Blue bar represents 95% CI

Although we did not specifically look at the grading of appendicitis by histopathologists, we did examine the pathology reports of all patients involved in the study. We found that of all the appendix samples sent for histology, the term 'perforated' or 'perforation' was mentioned in 17 of 190 reports. Sixteen of these reports were of appendixes in group 4. As the aim of our study was not to evaluate any correlation between the surgeon grading and microscopic pathological grading, we did not actively ask the reporting pathologist to provide a grading on the scale we have used for intra-operative grading.

Discussion

Traditionally, the pathogenesis of appendicitis has been accepted as being caused by direct luminal obstruction causing inflammation, leading to pressure necrosis and full thickness gangrene which may eventually result in perforation.[4] As a result, traditional surgical teaching dictates that acute appendicitis should be treated as a surgical emergency to prevent the sequelae of peritonitis, sepsis and death associated with a perforation.[10] This is being disputed in the modern literature. It is now thought that in addition to luminal obstruction, genetics, environmental influences and infections may also predispose to appendicitis.[5] The aforementioned causes of appendicitis may also have a different natural history of disease progression (i.e. time to perforated appendicitis) to what has traditionally been accepted. It is this theory that may explain why some patients present with a disease process more likely to result in a perforated appendicitis whereas others may be safely managed in a non-operative manner. Differentiating between these groups of patients may prove to be a challenge in clinical practice.[6] For this reason, our study is important in determining beyond what period of time it is unreasonable to wait from the onset of symptoms to perform an appendicectomy.

Table 1 Dunn's multiple comparison test between two groups

Dunn's multiple comparison test	Difference in rank sum	Significant? $p < 0.05$?	Summary
< 24 vs 24–48	− 9.624	No	ns
< 24 vs 48–72	− 19.49	No	ns
< 24 vs 72–96	− 68.41	Yes	***
< 24 vs > 120	− 49.91	Yes	***
24–48 vs 48–72	− 9.862	No	ns
24–48 vs 72–96	− 58.79	Yes	***
24–48 vs > 120	− 40.29	Yes	***
48–72 vs 72–96	− 48.92	Yes	**
48–72 vs > 120	− 30.43	Yes	*
72–96 vs > 120	18.50	No	ns

ns not significant

*$p \le 0.05$; **$p \le 0.01$; ***$p \le 0.001$

Our study confirms the anecdotal evidence that in appendicitis, a strong correlation between time and disease progression to perforation exists particularly beyond 72 h of symptom duration, as demonstrated by Fig. 3. This is of clinical significance as if a patient presents with nearly 72 h of pain, an operation should be scheduled as urgent as increasing the waiting time to greater than 72 h after onset significantly increases chance of perforation. The correlation demonstrated may suggest that there is a single dominating mode of pathogenesis in our patient cohort leading to perforation. This study has also confirmed that inflammatory markers are seen to rise as the macroscopic appearance of the appendix worsens (Fig. 2a, b). Whilst we believe it is prudent to consider the duration of symptoms in predicting the severity of appendicitis, CRP has been found to be of use in patients with prolonged symptoms; we identified 25 patients with a duration of symptoms over 72 h and a non-perforated appendicitis. In these patients, we found the median CRP to 32 mg/L, when compared to those with symptoms over 72 h and a perforated appendicitis who had a median CRP of 218 mg/L. Unpaired *t* test to compare these two values yielded a p value < 0.0001, indicating the usefulness of CRP in differentiating between perforated and non-perforated appendicitis in patients with symptoms over 72 h (Table 2).

It should be noted that the range in duration of symptoms recorded was largest in the perforated group (15–370 h). On examining the patients in the lowest quartile of length of symptoms in the perforated group, no discriminating demographic or clinical features were found. It could be that patients in this group have an underlying cause of appendicitis different to the majority of other patients with appendicitis that may cause perforation in a shorter amount of time. Others have made a similar observation.[11] The authors therefore emphasise that caution should be practised if using duration of symptoms alone as a single factor in predicting severity of disease, and appropriate consideration should be given to physical examination, laboratory data and imaging when assessing the need for appendectomy.

Our study did not examine patients with appendicitis who had not undergone operative management. Further study of

Table 2 Comparison between perforated and non-perforated groups at over and less than 72 h. *p* values were calculated using unpaired *t* test

	Sx < 72 h and no perforation	Sx < 72 h with perforation	*p* value from *t* test	Sx > 72 h and no perforation	Sx > 72 h with perforation	*p* value from *t* test
Number	111	18		25	36	
Median CRP (mg/L)	19	97	0.0079	32	218	< 0.0001
Median WCC ($\times 10^9$/L)	13	16.7	0.0271	10.65	14.2	0.4378
Median age	30	36		34	49	

this group of patients may in future guide us as to which patients may be treated conservatively or in an ambulatory manner. With this in mind, it should be mentioned that a number of papers in the past 12 months have been published regarding the management of appendicitis with antibiotics. There has been an RCT looking at antibiotic treatment versus surgery in 'uncomplicated' appendicitis. Seventy-two percent of those treated conservatively did not require surgery but 27% had a further episode of appendicitis within 12 months and required surgery.[12] This is still not classed as standard management in the UK, or in our unit. It is also important to note that only patients with CT-proven uncomplicated appendicitis were enrolled onto the study.

On examining the pattern of pre-operative imaging used in this study, patients in group 4 had the highest proportion of pre-operative CT scan. This may be due to these patients presenting with a prolonged duration of symptoms leading the clinician to consider diagnoses other than appendicitis.

The results of this study should be considered in light of its limitations. The data examined was from a single institute; therefore, the results may not be directly comparable to that of other institutes where there is a higher frequency of use of cross-sectional imaging and/or clinical scoring systems in diagnosing acute appendicitis. In addition, the study solely takes into account the duration of symptoms and does not take into account any in-hospital delays that may lead to a potentially worse outcome. Four other studies have however demonstrated that in-hospital delays seldom lead to an adverse outcome at 30 days post-operatively, in both adults and children.[13–16] This is likely to be because patients presenting with a severe grade of appendicitis (groups 3 and 4) are more likely to be operated on sooner as a result of the clinician's ability to recognise the severity of their symptoms. Often, patients who experience in-hospital delays may have been placed on antimicrobial treatment which may alter the course of disease progression in appendicitis. With this in mind, our study implies that pre-hospital delays may increase the chance of a patient presenting with perforated appendicitis. Clinicians should therefore give appropriate emphasis to the duration of symptoms prior to the presentation when managing appendicitis.

Table 3 The number of patients who underwent pre-operative imaging is outlined above

	Macroscopic grade of appendicitis				
Pre-operative imaging	0	1	2	3	4
Computed tomographic scan	1	10	17	11	33
Ultrasound Scan	1	1	0	0	0

The adverse outcomes associated with perforated appendicitis have been well documented and include a longer length of stay and higher chance of post-operative complications.[17] Busch et al. found that perforation is associated with a higher re-intervention rate and prolonged hospital stay.[18] Bhangu et al. also determined that delays beyond 48 h in hospital were associated with an increased risk of surgical site infections and adverse events at 30 days.[8]

A review of litigation claims to the NHS Litigation Authority in the UK of all cases relevant to appendicitis between 2002 and 2011 revealed that delayed diagnosis and delay in performing operation accounted for 10 and 9%, respectively, of those litigation claims made with regard to emergency appendicectomy.[19] Seventy percent of claims made regarding delay in performing an operation were successful, commanding a median pay out of £35,154 (44,000 USD). With this in mind, surgeons should be weary of delaying operative management once the diagnosis has been made, particularly if the duration of symptoms is over 72 h as shown in our study.

Conclusion

Whilst there is much recent debate over the pathogenesis of perforated appendicitis, our study suggests that the majority of patients with a perforated appendicitis have had symptoms for over 72 h, suggesting that time is strongly related to the risk of a perforated appendicitis, particularly past the 72-h point. Combined with the increased chance of post-operative complications and litigation risks associated with patient's management being delayed, the authors strongly recommend that patients approaching the 72-h mark should undergo operative management as soon as it is safe to do so. The authors also stress that despite there being no statistically significant increase in risk of perforation up to 72 h, we are not implying that it is safe to delay a patient's operative management up to 72 h.

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Author Contributions Mr. Mohammed Elniel: Data collection and drafting the manuscript. Ms. Jennie Grainger: Concept design, data collection, and contribution to conclusion and discussion of the manuscript. Dr. Edward J. Nevins: Statistical analysis of the data and main contributor to the results section. Mr. Nikhil Misra: Proofreading the manuscript and supervisory role. Mr. Paul Skaife: Proofreading the manuscript and supervisory role.

Compliance with Ethical Standards The data used in this manuscript has previously been used in the following two oral presentations: 1. ASGBI meeting (Belfast) May 2016 International Surgical Congress (Belfast) under the title: "Exploring an association between the duration of symptoms and intraoperative findings in the context of appendicitis". 2. European Congress of Trauma and Emergency Surgery (Bucharest, Romania) May 2017 under the title: "When is it time critical to operate in appendicitis".

Conflict of Interest The authors declare that they have no conflict of interests.

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