

Computerized tomography scan in acute appendicitis with eventual negative appendectomy

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Journal of Clinical and Translational Research

Dear Dr Chia,

Reviewers have now commented on your paper. You will see that they are advising that you revise your manuscript. If you are prepared to undertake the work required, I would be pleased to reconsider my decision.

For your guidance, reviewers' comments are appended below.

If you decide to revise the work, please submit a list of changes or a rebuttal against each point which is being raised when you submit the revised manuscript. Also, please ensure that the track changes function is switched on when implementing the revisions. This enables the reviewers to rapidly verify all changes made.

Your revision is due by May 11, 2021.

To submit a revision, go to <https://www.editorialmanager.com/jctres/> and log in as an Author. You will see a menu item call Submission Needing Revision. You will find your submission record there.

Yours sincerely

Michal Heger
Editor-in-Chief
Journal of Clinical and Translational Research

Reviewers' comments:

Reviewer #1:

- * You state: «and 76 (87.4%) patients had right lower abdominal pain." In other words, 11 patients did not have right lower quadrant pain, but still underwent appendectomy. Why were these operated? Why were these included? Your study should only include patients operated for suspected appendicitis.
- * You need to more clearly state how many patients were operated for clinically suspected appendicitis or for other diseases.
- * "All 87 patients had a Glasgow coma score of 15 at presentation". This is a trauma score and has nothing to do with the herein described pathology. Delete.
- * What were the final diagnosis of the 87 patients? How many had gynecological disease? Other diseases? This is important to know, as radiologist on second review found other pathology in 57%.
- * How did the initial radiology report differ from the review of the CT?
- * What was the interrater reliability between the two radiologists? You need to show this data. How did you decide in conflicting results?

Your manuscript would clearly gain strength if you include all 2000 patients and compare CT of positive and negative appendectomies. Was CT scan more often performed in your 87 patients as compared to the others?

* Conclusion: "Our study shows that patients with temperature $>38^{\circ}\text{C}$ or $<36^{\circ}\text{C}$, rebound tenderness, elevated total white blood cell count and neutrophilia are more likely to be offered appendectomy without a CT scan and....". This is not correct, as you only included patients with negative appendectomy. You did not include all patients with CT and positive appendectomy. You need to focus the discussion more on the role of CT and what to do if CT shows no appendicitis, but the clinical situation is highly suspicious of appendicitis.

Reviewer #2: Thank you for an interesting article about the negative appendectomy. The manuscript is well structured and clear. Still have some comments:

1. I suggest the term appendectomy, not the appendicectomy.
 2. Could you describe more about the indications for CT scan. Do you perform an ultrasound for all patients? Maybe you perform CT scan that an appendix is not visible during ultrasound visualization? What are your criteria? Please specify.
 3. Moreover, please explain, why you do not perform CRP for inflammation? It is cheap laboratory test.
 4. The English language, sentences structures must be checked and edited by native speaker.
-

Authors' response

Reviewer #1:

Comment 1: You state: «and 76 (87.4%) patients had right lower abdominal pain." In other words, 11 patients did not have right lower quadrant pain, but still underwent appendectomy.

Why were these operated? Why were these included? Your study should only include patients operated for suspected appendicitis.

Response 1: Many thanks for this comment. All included patients were operated for suspected acute appendicitis. Indeed, abdominal pain is the cardinal symptom that brings the patient to hospital, and thus core basis for diagnosis of acute appendicitis. All our patients indeed had abdominal pain that brought to hospital and emergency department admitted them for further investigations. We intended to state ‘migratory pain’, as this ‘migratory right lower abdominal pain’ is a symptom that scores 1 point in Alvarado system. Patients with no history of ‘migration of pain to right lower abdomen’ are scored zero points. We have edited the statement in results section and also Table 1. Now the statement reads as – “22 (25.3%) patients experienced anorexia, 40 (46.0%) patients experienced nausea or vomiting, and 76 (87.4%) patients had migratory right lower abdominal pain”.

Comment 2: You need to more clearly state how many patients were operated for clinically suspected appendicitis or for other diseases.

Response 2: Many thanks for this suggestion. As such all the patients that we have included in this study were operated for suspected acute appendicitis, but eventual histology was normal. To enhance clarity, we have edited the second paragraph in method section. Now the statement reads as – “For this study, we reviewed histology reports of all patients who underwent an appendectomy for suspected AA”.

Comment 3: "All 87 patients had a Glasgow coma score of 15 at presentation". This is a trauma score and has nothing to do with the herein described pathology. Delete.

Response 3: Many thanks for this suggestion. Glasgow coma score (GCS) represents ‘altered mental state’. Altered mental state is a subjective concept and GCS provided objectivity to this clinical symptom. The recent Sepsis-3 criteria advocates use of qSOFA score (quick SOFA score) for easy assessment of a patient in sepsis. The three elements of qSOFA score includes GCS, respiratory rate and systolic blood pressure. We included GCS in our manuscript for completion purpose. However, since GCS is traditionally associated with trauma, and this can generate confusion. We have changed GCS to – “altered mental state”. Now the statement in first paragraph of results reads as – “None of the 87 patients had altered mental state.” In addition, we have edited the Table 2 data variable and changed it from Glasgow coma score to ‘Normal mental state’. Our initial intent was to compute qSOFA score, as it is more relevant to recent sepsis-3 guidelines. However, as we had no patient with altered mental state, we decided not to compute the qSOFA score.

Comment 4: What were the final diagnosis of the 87 patients? How many had gynecological disease? Other diseases? This is important to know, as radiologist on second review found other pathology in 57%.

Response 4: Many thanks for this comment. This study included 87 patients who had suspected acute appendicitis, were operated, and histology was normal. As the median hospital stay was 2.0 days, and histology results are only known at a later date, all the 87 patients were discharged from hospital with diagnosis of ‘acute appendicitis’. None of the patients was readmitted or diagnosed with alternative pathology at one month clinic follow-up. We have added this in method section – “All patients were reviewed in outpatient clinic at one-month post-operative, and none of the patients was diagnosed with alternative diagnosis.” It is possible that some patients might have had nonspecific abdominal pain, self-limiting gynecological condition etc, but these were not diagnosed at one month follow-up. The radiology review for ‘other incidental pathology’ yielded other incidental pathology in 27 patients (out of 47 patients with CT scan done). The incidental pathology included kidney

cyst, liver cyst, liver hemangioma, spleen cyst, pancreatic cyst, indeterminate liver lesion, ovarian cyst, and gallstones. Some patients had multiple incidental pathologies detected.

Comment 5: How did the initial radiology report differ from the review of the CT?

Response 5: CT scan was done for 47 patients with suspected acute appendicitis. The reporting duty radiologist is (possibly positively) biased with the clinical information provided, and thus likely to report acute appendicitis. This is more relevant if subtle imaging features are considered e.g., wall thickening, lumen diameter etc. Thus, we have discussed the embargo surrounding imaging features like – mildly prominent appendix, dilated appendix, threshold for dilated appendix (6mm up to 10mm), etc. We have enhanced the discussion and updated with supporting data by including a similar study published in 2005 - Daly CP, et al. Incidence of acute appendicitis in patients with equivocal CT findings. AJR Am J Roentgenol. 2005 Jun;184(6):1813-20. PMID: 15908536.

Daly CP, et al recruited two radiologists to review the equivocal CT scan cases, to reassess appendiceal size, presence of right lower quadrant stranding, fluid, or an appendicolith. The reviewers' findings were correlated with surgical pathology reports and clinical follow-up. Authors reported that 119 (69%) of 172 patients with equivocal CT scans did not have appendicitis. For reviewers 1 and 2, respectively, appendicitis was present in five (14%) of 36 and six (13%) of 47 patients who had isolated appendiceal diameter less than 9 mm, and in 11 (52%) of 21 and in 10 (50%) of 20 patients who had isolated appendiceal dilatation equal to or greater than 9 mm. If a normal diameter appendix (< 6 mm) was visualized in a patient who had right lower quadrant stranding or fluid, appendicitis was present in only one (17%) of six and in four (27%) of 15 patients for reviewers 1 and 2, respectively. If the appendix could not be identified but there was right lower quadrant stranding or fluid, appendicitis was present in seven (37%) of 19 and in eight (53%) of 15 patients.

We have added the following in discussion - In 172 patients with equivocal CT scan in AA patients, Daly CP et al. has recruited two radiologists to reassess appendiceal size, presence of right lower quadrant stranding, fluid, or an appendicolith [29]. Authors reported that 119 (69%) of 172 patients with equivocal findings on CT scans did not have AA.

Comment 6: What was the interrater reliability between the two radiologists? You need to show this data. How did you decide in conflicting results?

Response 6: Thanks for this comment. We asked two radiologists for comments; however, we formulated a unified opinion by internal discussion and agreement. We have included this in study methodology - In cases of discordance, a consensus was reached by internal discussions and mutual agreement between the two radiologists. For this study, we compiled the unified opinion of the two independent radiologists for direct comparison of a unified post-operative opinion with pre-operative imaging. We have added this in limitation section as – “In addition, we combined the report of both radiologists to formulate a unified report. Thus, we were unable to report interrater reliability among the two radiologists.”

Comment 7: Your manuscript would clearly gain strength if you include all 2000 patients and compare CT of positive and negative appendectomies. Was CT scan more often performed in your 87 patients as compared to the others?

Response 7: Many thanks for this valuable comment. This study was designed to include patient population defined as having histological normal appendix and thus the data of 2000 patients was not relevant and not retrieved. Having data of all patients operated for appendectomy will help identify the false negatives (CT scan is falsely negative, patient had histology proven appendicitis). With the changes (adopted in 2019) in human biomedical and

research act (HBRA) in Singapore, at this stage it is not possible to review the medical records retrospectively and thus, we will not be able to provide this data. However, senior author is working in Tan Tock Seng Hospital since 2008 and has an overview of imaging in patients with acute appendicitis. In general, CT scan is done in more than half of inpatients admitted via right iliac fossa pain pathway for three reasons: (1) right colon diverticular disease is common locally (Ref 19 in manuscript, Tan KK et al.), (2) one extra day of hospitalization if more expensive than the cost of CT scan and thus there is net value gain in doing CT scan, and (3) Morbidity of normal appendectomy is similar to morbidity for appendectomy for acute appendicitis (e.g., post-operative adhesions, etc.) (Ref 3 in manuscript, Baird DLH et al.). In a separate study reporting on 22 patients with diverticular disease of appendix, we reporting 17 patients (77.3%) having CT scan done prior to appendectomy ([Diverticular Disease of the Appendix Is Associated with Complicated Appendicitis \(karger.com\)](#)). We have added the study limitation as – “We did not collect data from patients with histology proven appendicitis, and unable to comment on true positive and false negative rate of CT scan.”

Comment 8: Conclusion: "Our study shows that patients with temperature $>38^{\circ}\text{C}$ or $<36^{\circ}\text{C}$, rebound tenderness, elevated total white blood cell count and neutrophilia are more likely to be offered appendectomy without a CT scan and....". This is not correct, as you only included patients with negative appendectomy. You did not include all patients with CT and positive appendectomy. You need to focus the discussion more on the role of CT and what to do if CT shows no appendicitis, but the clinical situations is highly suspicious of appendicitis.

Response 8: Thanks for this comment and we agree with the suggestion that we should be cautious in such conclusion as false negatives as well as true positives of CT scans are unknown in the absence of data of 2000 patients. As the study aims to include patient population with normal histology following appendectomy, we have edited the conclusion section and also a limitation of the study. We have added the following statement in discussion section – “In patients operated for suspected AA with eventual normal histology, temperature $>38^{\circ}\text{C}$ or $<36^{\circ}\text{C}$, rebound tenderness, elevated total white blood cell count and neutrophilia are associated with clinical decision for appendectomy.”

In situations where clinical situations are highly suspicious of appendicitis, but CT scan is normal (false negative CT scan), surgeons must proceed with clinical judgment. Fortunately, such instances will be rare with better quality of imaging and standardized reporting. Thus, our study adds to the current body of evidence. We have added the following in limitation section – “In patients with clinical features suspicious of AA but normal CT scan, clinician judgment should take precedence and management guided by local protocols, resources, as well as experience.”

Reviewer #2: Thank you for an interesting article about the negative appendectomy. The manuscript is well structured and clear. Still have some comments:

Comment 1: I suggest the term appendectomy, not the appendicectomy.

Response 1: Ok. We have edited as per your suggestion.

Comment 2: Could you describe more about the indications for CT scan. Do you perform an ultrasound for all patients? Maybe you perform CT scan that an appendix is not visible during ultrasound visualization? What are your criteria? Please specify.

Response 2: Many thanks for this very valid and clinically relevant comments. We have included in method section - Our hospital does not have paediatric and gynaecological

services and thus abdominal ultrasound and magnetic resonance imaging (MRI) are rarely done in context of AA. Also, CT scan is available round the clock and US/MRI scan only available during office hours and on weekdays. Thus, by and large all patients receive CT scan. Sometimes, locally we casually chat that in ABC of resuscitation, 'C' means CT scan.

Comment 3: Moreover, please explain, why you do not perform CRP for inflammation? It is cheap laboratory test.

Response 3: Many thanks for this comment. We agree that CRP is cheap and readily available test. Locally for a subsidized patient, cost of CRP is below 10 SGD and for a private patient it is below 20 SGD. Currently, the emergency department right iliac fossa pain care pathway includes Alvarado score as the main clinical decision-making tool. CRP test is not bundled in the current serological tests for patients with right iliac fossa pain. Sporadically, some patients have CRP done based on the surgeon in charge managing the case. We have included this as the study limitation - We did not routinely do C-reactive protein, serum procalcitonin, or serum albumin in patients presenting with right iliac fossa symptoms and hence unable to report all the inflammatory markers.

Comment 4: The English language, sentences structures must be checked and edited by native speaker.

Response 4: We have checked. We have also run the manuscript with English editing software.

2nd Editorial decision
24-Apr-2021

Ref.: Ms. No. JCTRes-D-21-00026R1

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Dear authors,

I am pleased to inform you that your manuscript has been accepted for publication in the Journal of Clinical and Translational Research.

You will receive the proofs of your article shortly, which we kindly ask you to thoroughly review for any errors.

Thank you for submitting your work to JCTR.

Kindest regards,

Michal Heger
Editor-in-Chief
Journal of Clinical and Translational Research

Comments from the editors and reviewers:

Reviewer #1: no comments

Reviewer #2: All the questiones have been answered.