
Dear Editors and Reviewers:

Thank you for your letter and for the reviewers' comments concerning our manuscript entitled "Revisiting delay to appendectomy for patients with acute appendicitis: Why the delay and is it worth the delay?" (Manuscript NO.: 66049).

Those comments are all valuable and very helpful. I have studied comments carefully.

The main responds to the reviewer's comments are as following:

Responds to the Editorial requests and reviewer's comments:

Reviewer 1:

Comments: This is an interesting review article regarding the important topic for general surgeons. The title, abstract, key words, and the literature review with division into subheadings are correct. The references are appropriate. Figure 1 clearly shows timeline of the key events in the history of the research on surgery delay in acute appendicitis. The review article is comprehensive and contains a lot of informations. Summary of all discussed article in the table could be considered by the author. The table should present the author's name, publication year, article type and design, number of enrolled patients and the most important conclusions. The author's opinion would on the current diagnostics and management in acute appendicitis would be interesting for readers. What about the current role of computed tomography in patients with acute appendicitis? I think that more information on this topic as well as information regarding association between surgery delay and the more frequent CT use should be presented in this article.

Responses:

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1. Thanks very much for your good suggestion. According to the comments, I have summarized relevant references in three tables.
 2. Regarding CT in AA, many excellent reviews and clinical guidelines (WSES) have discussed its advantage and disadvantage. Association between surgery delay and the more frequent CT use is also a debate, in the primary edition of my review, this topic has been touched upon but scatter in sections “Atypical clinical presentation”, “Coronavirus disease 2019 pandemic”, “To diagnose AA precisely”, etc., because of the relationships between them. Therefore, I'm not going to list this topic separately but still thanks for your advice.

Reviewer 2:

Comments: This is a descriptive (not a systematic) review. The topic of "delay in appendectomy" is of great interest to general surgeons. As highlighted in this review, most of the current studies are of low level of evidence and bear contradictory conclusions. However, there is general agreement that delaying appendicectomy -in nonperforated appendicitis-for 12-24 hours does not lead to increased morbidity and mortality. This is a good descriptive review. However, the manuscript contained several sentences that need revision for clarity. I have placed some suggestions to some of the headings and subheadings.

Response: Thank you very much for your comments and suggestion, and I have studied comments carefully and revised as following. And thanks for many language issues pointed out by the reviewer. As being a non-native English speaker, it is difficult for me to write an article without language defects, therefore, according to the author guideline,

the article have been sent for edition by AJE, and hope that my article will meet with approval.

I have the following comments: Title: can be shortened to "Revisiting delayed appendectomy in patients with acute appendicitis".

Responses: The title has been shortened to "Revisiting delayed appendectomy in patients with acute appendicitis".

Abstract: 1) line 2: change 'nonselective' to 'nonelective'. 2) line 7: change 'many factors will emerge' to 'many factors can cause delay in the surgical intervention'.

Responses: Revised as comments.

Introduction: 1) line 7: sentence 'Because of the urgency of the diagnosis and associated adverse effects with perforation, traditionally, it is believed that appendectomy should be performed expeditiously after a diagnosis is made.' needs to be rephrased for clarity.

Responses : Revised as "It is generally thought that untreated appendicitis will eventually progress to perforation, with an associated drastic increase in morbidity and mortality, leading to the traditional concept that appendectomy should be performed expeditiously after a diagnosis is made."

2) line 9" Change 'from the last 2 decades' to 'in the last 2 decades'.

Responses: Revised as comments.

3) It is worth mentioning the introduction section the way review of the published literature was done and what were the 'search words' and the search engines used.

Responses: According to the reviewer's comments, a literature search strategy section was added into the acknowledgement but not into introduction.

Under 'Spontaneous resolution': Line 3 from the bottom, sentence 'In addition, the incidence of AA decreased overall, which was mainly attributed to nonperforated but not perforated AA , suggesting that a disconnect exists between the two types of appendicitis[6].' could do with rephrasing for clarity.

Responses: Revised as “In addition, time series analysis found that the incidence of AA decreased overall, which was mainly attributed to nonperforated but not perforated AA, suggesting that a disconnect exists between the two types of appendicitis. ”

Page 4, line 3: Sentence 'No mater presents as phlegmonous (pus-producing) or advanced inflammation (but without gangrene or perforation) that needs appendectomy, ..' Poor English. Please revise for clarity.

Responses: Revised as “The reversible form is simple inflamed appendicitis, which can present as phlegmonous (pus-producing) or advanced inflammation (but without gangrene or perforation) that needs appendectomy or, alternatively, as mild inflammation that can resolute either spontaneously or with antibiotic therapy; this form of AA will not proceed to gangrene and perforation.”

Page 4, last sentence line 3 from the bottom ' No intra-abdominal abscesses or other major complications resulted from delayed appendectomy in patients randomized to antibiotic treatment.' Poor English; rephrase for clarity.

Responses: Revised as “There were no intra-abdominal abscesses or other major complications associated with delayed appendectomy in patients randomized to antibiotic treatment”.

In the subheading of 'Successful non-operative management', it is worth mentioning a

brief account of the recommended steps in the NOM policy.

Responses: Although there has a general steps in the NOM policy depicted in figure 1, that is begin with an uncomplicated AA diagnosis was established, then antibiotics were given, then surgery or follow-up were carried out according to the results of NOM, the detailed steps diverse across studies, and many challenges exist, as I have discussed in this review, therefore, recommended steps in the NOM policy was not further summarized.

Under 'Lack of medical resources': Page 9, para 2: sentence 'A surgeon taking a call at home may feel obligated to drive to the hospital to perform an emergency appendectomy in the middle of the night or on weekends to alleviate sleep deprivation among the surgeon and affiliated staff'. Poor English. Revise and rephrase for clarity.

Responses: Revised as “A surgeon taking a call at home may feel obligated to drive to the hospital to perform an emergency appendectomy in the middle of the night, thus requiring mobilization of the anesthesiologist and operating room nursing staff, leading to sleep deprivation of not only the surgeon, but affiliated staff”.

I am pleased to see you touched on the impact of Covid-19 pandemic on general surgical practice.

Responses: This pandemic has had a profound impact on all aspects, including in healthcare. It needs the joint efforts of all mankind to win.

Change subheading 'adverse events' to 'paotoperative complications'. Change subheading 'unsatisfaction of patients' to 'Dissatisfaction of patients'. Change heading 'Why conclusion inconsistent across studies' to 'Appraisal of current studies on delayed

appendectomy'. Page 18, subheading 'Grade the severity of AA correctly at presentation' to be changes to 'Correct severity grading of AA at presentation'.

Responses: Revised as comments.

Page 18, last sentence 'to increase strategy currently': Poor English, please revise for clarity.

Responses : Revised as “Currently, the way to improve the success rate of the nonoperative approach and to reduce the rates of perforation and negative appendectomy is mainly based on correct selection of patients with uncomplicated AA. In addition, identifying patients with uncomplicated AA who will progress to perforation maybe another feasible strategy”.

Page 20, line 4 from bottom, sentence ' Whether LA can decrease can not be determined'. Poor English. Please revise.

Responses : Revised as “whether LA can decrease the mortality after negative appendectomy, which was reported to be high mainly during the period in which OA was performed, is uncertain.”

Conclusion section, 1) Line 3: change 'many factors will emerge..' to 'many factors can cause delays in surgical intervention. 2) Line 6, change ' seeking a doctor' to 'seeking medical advise' 3) line 9, change 'inheritance' to 'inherent'.

Responses: Revised as comments.

Page 22, Line 2, sentence 'Therefore, with the aim of shortening the waiting time before appendectomy and improving the prognosis of this disease, in spite of ascertaining the causality between delayed and complicated AA and associated adverse effects, ' Revise

for clarity.

Responses: Revised as “Therefore, in order to shorten the waiting time before appendectomy and to improve the prognosis of AA, it is important to ascertain the causality between delayed and complicated AA and associated adverse effects and to develop new biomarkers and advanced imaging technology”.

I am not sure why you included NOTES and endoluminal surgery as advantageous therapy strategy in reducing delay in surgery.

Responses: Here I not only mean to reduce delay in surgery but also to improve the outcomes of AA.

4 LANGUAGE QUALITY

Please resolve all language issues in the manuscript based on the peer review report.

Please be sure to have a native-English speaker edit the manuscript for grammar, sentence structure, word usage, spelling, capitalization, punctuation, format, and general readability, so that the manuscript’s language will meet our direct publishing needs.

Response: The language issues listed on the peer review report have been revised. As being a non-native English speaker, it is difficult for me to write an article without language defects, therefore, according to the author guideline, the article have been sent for edition by AJE, and hope that my article will meet with approval.

I appreciate for Editors/Reviewers’ warm work earnestly, and hope that my article

will meet with approval.

Once again, thank you very much for your comments and suggestions.

Yours sincerely,

Jian Li