

19th June 2021

Dear Editor in Chief

World Journal of Gastrointestinal Surgery

Re: Manuscript NO: 68310, Acute Appendicitis – Advances & Controversies

Many thanks for seeking peer reviews for our manuscript. We appreciate the time and expertise of peer reviewers. We are thankful to Chief Editor, as well as editorial team for granting extension of 5 days to submit the manuscript. The task of revision was challenging as we had to meet the expectations of both reviewers. We hope the edits are acceptable not only in content but also in format and layout of the manuscript. Please find the point-by-point response to the comments and have made edits in the manuscript.

Reviewer # 1

Comment 1: The title, abstract and key words clearly match the goal of the manuscript. The authors mention 'contact less' diagnosis within the core tip paragraph. Whilst I understand the essence of the statement, I would advise caution with this remark. This implies to a reader that the authors are suggesting that patients could undergo an imaging modality prior to being examined by a competent medical practitioner.

Response 1: We thank you for your detailed analysis of our manuscript and are humbled by your assessment. As rightfully mentioned, we agree that the nuance of 'contact less' is misleading and we have revised the "core tip" section. It is now 97 words.

Many controversies exist for the management of acute appendicitis (AA). Imaging modalities complement the clinical examination in AA diagnosis. Various imaging features of different imaging modalities should be considered to reduce diagnostic inaccuracies. Various diagnostic scoring systems augment clinical judgment, but uncertainty exists about the best score. Non-operative management of both uncomplicated and complicated AA is possible and reasonable,

especially during the COVID-19 pandemic. Intra-operative techniques of securing the base of the appendix stump via suture, clips, or stapling devices are all debated for superiority. Adjuncts and novel treatment ideas using endoscopic retrograde appendicitis therapy are emerging.

Comment 2: Methods - who screened the manuscripts?

Response 2: Thank you for the comment. We have noted the missing information and have edited as follows:

A search of relevant articles on PubMed, OVID/MEDLINE, and Web of Science was conducted on 6 May 2021 for literature published in English by Teng TZJ, Thong XR, and Lau KY. Disagreements were resolved by mutual discussions and consensus with senior authors Balasubramaniam S and Shelat V.

Comment 3: Scoring systems - this section seems unnecessarily word heavy with a large amount of statistics being presented within the paragraphs. This section would be better served by describing each of the scoring systems and then presenting the specificity/sensitivity values within a table. It is too easy for a reader to lose interest when reading a long list of statistics within a paragraph.

Response 3: Thank you for the comment. We agree that the manuscript can be crystalized and have provided supporting statistics in the form of a table attached in an effort to keep the readers' interests while reading. Table 1 is added to the manuscript. Table provides summary of scoring systems with pertinent clinical utility. Also, in line with general comment that manuscript is too long and could be broken down into a few manuscripts, we have discussed this. Overall, as a group we feel we want to retain broad themes relevant to controversies of acute appendicitis. Hence, we have decided to trim various sections, including the section on scoring systems. All the scoring systems are grouped in one paragraph. Overall, this section is significantly shortened.

Comment 4: I feel that an additional paragraph is required regarding the significant differences in practice surrounding the use of imaging for appendicitis throughout the world. For example, within the UK, CT scans are rarely used for the diagnosis in the under 50 population. I

acknowledge that the authors did state 'CT scan may be a more appropriate first-line investigation in overweight or elderly patients'.

Response 4: Thank you for your comment. We agree clinical practice differs across different countries. In fact, it is this diverse practice that has motivated the author to summarize the existing evidence base and discuss the controversies. The senior author recently wrote two letters to editors with regards to two manuscripts on AA – one for Journal of Surgical Research (PMID – 32917388) and another for ANZ Surgery (PMID-33710733). In USA, the practice is predominant to use stapling devices for stump control. The insurance driven economy justifies it as safe and effective policy. In Australia, the local culture puts emphasis on clinical diagnosis and thus they report about 30% negative appendectomy rate. We have added a paragraph on the limitations of imaging based on local protocols, financial and global logistical constraints.

Use of imaging across countries

Imaging improves diagnostic accuracy at a financial cost. Patients from lower-income countries may not have accessibility and affordability to CT scans and MRI scans. A study of the management of AA in 44 different countries by Gomes et al. revealed that CT scans were done more liberally in accordance with the countries' income level (High-income countries 38%, Upper-middle income countries 23%, Lower-middle income countries <8%)^[58]. Within a country itself, there are discrepancies on which modality of imaging to consider first as well. This may be due to the proportion of special populations in the country (obese, children, pregnant women), the logistical constraints of the hospital (primary vs tertiary hospital) as well as the availability of radiologists' opinion (working hours, overnight shifts, public holidays)^[59]. While prudence needs to be exercised to request imaging to aid AA diagnosis, a refusal or rejection of imaging request on the pretext of "appendicitis is a clinical diagnosis, and please do appendectomy if clinically you feel so" or "do a serial examination and it will reveal itself over next few days" etc. from radiology colleagues is unacceptable. In our experience, liberal imaging policy is associated with low NAR. In a local audit of 2603 appendectomy patients, NAR was 3.34% (n=87)^[60]. The unmet need remains the lack of uniform standardized criteria that define imaging diagnosis of AA. In particular, the imaging features of the prominent or dilated appendix can be subjective and international collaboration is needed to define thresholds for AA imaging diagnosis.

In addition, we have re-grouped the subheadings on imaging section too and trimmed down the content.

Comment 5: The authors state that MRI is used as a first line modality in children for the diagnosis of acute appendicitis. This should be referenced. It should also be expanded on the logistical issues regarding MRI scans, particularly out of hours. This should include the challenges of performing MRI scans on younger children with regards to staying still and claustrophobia.

Response 5: Thank you for the comment. We have noted the need to reference the use of MRI in children in the paragraph and have provided the systematic review on MRI in paediatric appendicitis by Moore et al as reference. We have also taken your comment on providing other constraints to the use of MRI in children as stated. The following is added -

A meta-analysis of 11 studies has reported that an MRI scan improves diagnostic accuracy, reduces time to appendectomy, NAR, and aids in alternative diagnosis. Other considerations for children include an incomplete MRI due to fear from claustrophobia, staying still, and noise emitted from MRI. These concerns can be addressed with child and parental counseling or sedation^[55].

Comment 6: The management section is very similar in that it is a long list of statistics from other studies. Whilst I understand the reason for this, it makes this overall paper difficult to read.

Response 6: Thank you for your comment. We do agree that the management section is elaborate. As appendicitis is a vast topic, this is partly expected. We have made active and extensive efforts to edit and trim down the content in the current version. Hope that now the manuscript is at least 'not difficult' or 'easier' to read and follow.

With the added table and figures, the outlay of manuscript is now more reader-friendly. We have also significantly trimmed the section on diagnostic dilemma, differential diagnosis and special situations.

Comment 7: The overall impression of this manuscript is one that has been well written and well researched. However, I feel that a narrative review should offer more than paragraph after paragraph of listed statistics. The authors would be well placed to narrate more around the issues, rather than list the statistical values (these can easily be placed in tables). This paper feels far too long and would have been better placed as 2 or 3 separate review articles.

Response 7: We thank you for your honest critique of the manuscript and are humbled by your impression that it is well written and well researched. To circumvent the issue of the paper being too lengthy, we have heeded your advice to reduce the ‘diagnostic’ and ‘management’ portions by reducing the statistics listed and providing this information in the form of visual aids. **Figure 1, 2 and Table 1 are added to reduce wordy lengthy paragraphs. The earlier version had 28 pages and 9266 words (excluding core tip and abstract section) while the current version has 19 pages and 7071 words (-23.7%).**

Reviewer # 2

Comment 1: It should be accepted for publication.

Response 1: We humbly thank you for your approval of our manuscript and are pleased to know that it has met the satisfaction of our colleague such as yourself.

We have removed a lot of content as recommended by reviewer 1 and hope this is acceptable to yourself as well. We have added a paragraph on “incidental findings’ It reads as below:

Two categories of incidental findings need discussion. Firstly, situations where intraoperative AA is established, but a separate incidental pathology is detected^[122]. In such instances, it is our opinion that a surgeon should proceed with an appendectomy and document the operative findings. The incidental pathology can be investigated and managed later. Secondly, situations where the appendix appears normal to visualization. Laparoscopy has an advantage in such situations; a surgeon can thoroughly explore the peritoneal cavity. If a definitive pathology is detected and the patient appropriately consented, the surgeon can proceed accordingly. It is debatable and controversial if a normal appendix must be removed, especially if another pathology is established. Our practice is to remove a “normal-appearing” appendix in the absence of other established diagnoses ^[123]. We do this for two reasons. Firstly, a “normal-

appearing" appendix may be an early AA. Secondly, removal of the appendix eliminates future diagnostic dilemmas for right iliac fossa symptoms.

Comments from Science Editor:

Comment 1. Title page: Author names should be written out first (as first name, middle name initial (with no period) and family (sur)name initial (with no period) and family (sur)name; with a hyphen included between the syllables of Chinese names); the corresponding author's E-mail address should follow the affiliation's ending period with a single space; please provide ORCID number of all the authors. Please provide one more Key-word.

Response 1: The authors names have been updated as per requirements: **Thomas Zheng Jie Teng, Xuan Rong Thong, Kai Yuan Lau, Sunder Balasubramaniam, Vishalkumar G Shelat.**

The corresponding email now follows the affiliation's ending period with a single space. ORCID numbers for all the authors have been added:

OCRID numbers

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An additional keyword has been added: *Advances*

Comment 2. The Core Tip should be limited to 100 words.

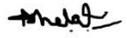
Response 2: We have limited the number of words to 95 words.

Comment 3. The Reference list should follow the journal style (For authors' names, the name of the first author should be typed in bold letters.

Response 3: We have formatted the reference list via the online editing tool on f6publishing as suggested on the portal. In addition, we have reduced the number of citations extensively too.

Thank you

Sincerely



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