

April 6, 2020

Jin-Lei Wang, Director

The Third Editorial Office Director

World Journal of Clinical Cases

Dear Dr. Wang,

Thank you for reconsidering our manuscript titled “**Clinical prediction of complicated appendicitis: a case-control study utilizing logistic regression**” for publication in your esteemed journal, *World Journal of Clinical Cases*. We wish to re-submit the revised version of our manuscript for your review. The manuscript ID is 54694 (Invited article).

We appreciate the reviewers’ invaluable comments, which have helped us improve our manuscript. We have provided point-by-point responses to each of the reviewer’s comments and describe the corresponding revisions. As per your instructions, changes have been indicated by underlined font in the revised manuscript.

We look forward to any further comments regarding our revised manuscript.

Sincerely yours,

Yosuke Sasaki, MD, PhD

Department of General Medicine and Emergency Care

Toho University School of Medicine, Omori Hospital

6-11-1 Omori-Nishi, Ota-ku

Tokyo 143-8541, Japan

Phone: +81-3-3762-4151

Fax: +81-3-3765-6518

Email: pqrstbb@yahoo.co.jp, yousuke.sasaki@med.toho-u.ac.jp

Responses to the Reviewers' Comments

Responses to comments from reviewer #1:

Comment 1:

This is a very-well written paper about a predictive potential of laboratory and non-laboratory markers with respect to differentiation between simple and complicated acute appendicitis. I commend authors on the paper presented and the amount of work done.

Response: Thank you very much for the supportive comment.

Comment 2:

The authors should consider using MeSH terms as keywords

Response:

Thank you for the comment. As per your suggestion, we selected the following MeSH keywords:

Abdomen, acute [C23.888.592.612.054.200]

Abscess [C23.550.470.756.100]

Appendicitis [C01.463.099]

C-reactive protein [D12.776.034.145]

Forecasting [I01.320]

Intestinal perforation [C06.405.469.557]

Comment 3:

"which is compatible with the findings of previous studies [Drake FT. JAMA surg 2014]", please consider a standard citation instead of [Drake FT. JAMA surg 2014], i.e. number 6.

Response:

We apologize for the typo. As per your instruction, this was revised to the appropriate citation style (i.e., reference number 6).

Comment 4:

The authors may be willing to check whether the units used when referred to CRP are correct, i.e. the authors are using mg/dL, whereas normally mg/L is used. If they are using it on purpose, it is alright, just make sure the unit they use is really the one they want.

Response:

Thank you for the thoughtful and kind comment. We agree that [mg/L] is widely used as a unit of serum CRP level. However, we found that [mg/L], [mg/dL], and [ng/mL] were all used as the units in previous studies we cited. Thus, we intentionally use [mg/dL] as the unit of CRP, as it is commonly used in Japanese (and probably in Asian) daily practice, and also a few previous studies used this same unit in the articles that we cited in our paper (references 12 and 15). On the evaluation of previously reported cut-off values, we carefully reviewed the units and converted them to [mg/dL].

Comment 5:

I am slightly uncomfortable with the formulation "early detection of patients with complicated appendicitis (CA)". In my opinion, if acute appendicitis is detected and treated timely, it may not progress into a complicated form. I suggest the authors rewrite this sentence.

Response:

We apologize for the unclear description. Although some patients have complicated appendicitis at the first encounter, we agree with your opinion

because timely diagnosis generally prevents the progression from simple to complicated appendicitis. As per your suggestion, we made the following revisions:

Abstract-background:

“differentiation of patients with complicated appendicitis (CA) from those with simple appendicitis (SA) has become increasingly important.”

Main text-Introduction:

“Because conservative management of AA will become more popular thanks to this recent evidence, differentiation of high-risk patients with complicated appendicitis (CA) such as gangrenous appendicitis, perforated appendicitis, or cases complicated with intra-abdominal abscess from simple appendicitis (SA) has become increasingly important.”

Comment 6:

Despite the authors admit it as a limitation to this study, the incidence of simple as well as complicated appendicitis were not controlled clinically by intra-operative and histopathology finding. This is a limitation to the study design that cannot be addressed. Although high, the sensitivity and specificity of CT is not (although almost) 100%. The authors should comment on why only 11.1% and 31.6% of patients with SA or CA, respectively, were operated on. Conservative treatment should be reserved only for special cases, it is not a standard of care. Please comment on this in discussion and mention briefly the role of conservative treatment of AA nowadays, if possible including reference to guidelines.

Response:

Thank you very much for the critical comment. We agree that we should discuss the conservative management of acute appendicitis because it differs from the

global standard and is not fully supported by clinical evidence. We added the following sentence to the Methods section:

“We ultimately included only patients who were diagnosed as AA by CT scans, instead of surgical or pathological findings because of the low proportion of the patients treated with appendectomy according to the management policy of surgeons at our hospital as an advanced medical center. (We will discuss the reason for the low proportion of operated patients in the Discussion section.)”

To explain the reason why only 11.1% and 31.6% of patients with SA or CA, respectively, were operated on, we added the following sentence to the Results section:

“Judgment on indication, reason, and selection of operated patients were based on the expert opinion of the surgeons on each individual case.”

Furthermore, we added the following sentences to the Discussion section to explain our current standard care of appendicitis, the role of conservative management, and our management strategy that differs from current global standards:

“We should note that our study was conducted under somewhat unique circumstance: Conservative management for AA that we routinely performed in our hospital is not the global standard management of AA (i.e., despite the fact that non-operative management of AA is increasingly accepted as an option of management of AA in some patents, such as those who prefer non-operative management or high-risk patients for operation ^[29], emergent or urgent appendectomy is still emergent or urgent appendectomy in most cases) ^[5].

However, because the evidence on conservative management and interval appendectomy is increasing, as mentioned above, our differentiation of SA and CA based on radiological findings as a surrogate for surgical or pathological findings may become more clinically significant.”

We also added a new citation as reference #29.

Comment 7:

I thank to the authors and kind regards to Japan from the Czech Republic!

Response:

Thank you very much for your thoughtful review. All of your comments helped us to significantly improve our manuscript.

Responses to comments from reviewer #2:

Comment 1:

This is a well designed, performed and written research paper on clinical prediction of complicated appendicitis.

Response: Thank you for the supportive comment.

Comment 2:

GFR (Abstract) - unlike other abbreviations, this one was not explained in full in the text.

Response:

We apologize for this oversight. As per your instruction, we changed “GFR” to “glomerular filtration rate (GFR)”.

Comment 3:

Categorization of contentious variables (Section Title, Page 12) - continuous is right.
contentious variables (Paragraph "Univariate Comparisons", Page 13) - see above.

Response:

We apologize for the careless typos. We changed “contentious” to “continuous” in both instances.

Comment 4:

All statistical analyses were performed using performed using Stata/IC software (Page 14) - "performed using" is presented twice. To be removed.

Response:

We apologize for the careless typos again. We removed the extra “performed using” from the sentence.

Comment 5:

In terms of the univariate analysis, our study showed that advanced age was a significant predictor of CA, which is compatible with the findings of previous studies [Drake FT. JAMA surg 2014] - Page 18. This kind of referencing is substandard. Please use a Reference number including a source into the Reference list.

Response:

We apologize for the typo. As per your instruction, this was revised to the appropriate citation style (i.e., reference number 6).

Comment 6:

Role of inflammatory markers in decreasing negative appendectomy rate: A study based on computed tomography findings Ebru (Reference 13) - how to explain "Ebru"? This word is absent in an original Title.

Response:

We apologize for the typo. “Ebru” was a typo due to a technical error caused by the reference management software we used. We manually removed “Ebru” from the reference list.

Comment 7:

Role of alvarado score and biological indicators... (Reference 14) - the word "Alvarado" should be capitalized.

Response:

We agree with you that Alvarado should be capitalized. We found that the typo is due to a technical error caused by the reference management software we used. We manually capitalized it.

Comment 8:

In the article, you present the definition of "Complicated Appendicitis". I think, it will be right to include a similar definition of "Simple Appendicitis".

Response:

Thank you for the comment. We agree with your opinion. As per your suggestion, we added the definitions of SA in the Methods section as follows:

“We divided the enrolled patients into SA and CA groups based on the findings of the CT scan and ultrasound as follows: Patients were diagnosed with SA if they were clinically diagnosed with AA and had radiological/sonographical findings compatible with appendicitis catarrhalis or appendicitis phlegmonosa such as swelling of appendicitis and inflammatory findings of adjacent adipose tissue without any of the following findings of CA;”

Comment 9:

I want to especially appreciate that the authors perfectly understand the limitations of their work. Reading the text, I immediately noted for myself that the radiological definition of the concepts of "simple" and "complicated" appendicitis can seriously differ from operational findings. And it was very nice to read the paragraph dedicated to this at the end of the article. Apparently, in a work based on clinical material, where the percentage of non-operated patients is large, the authors' approach should be considered the most correct.

Response:

Thank you very much for the supportive and important comment. To clearly explain why we had to define simple and complicated appendicitis based on radiological findings, we added the following sentences to the Methods section:

“We ultimately included only patients who were diagnosed as AA by CT scans instead of surgical or pathological findings because of the low proportion of the patients treated with appendectomy according to the management policy of surgeons at our hospital as an advanced medical center. (We will discuss the reason for the low proportion of operated patients in the Discussion section.)”

Furthermore, we added the following sentences to the Discussion section to explain our current standard care of appendicitis, the role of conservative management, and our management strategy that differs from current global standards:

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