

## ANSWERING REVIEWERS



July 09, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 3\_Manu\_appe\_perf\_R0.0.2\_final (No.111985)\_DECODE.doc).

**Title: A Novel Strategy for the Determination of Surgical Priorities in Appendicitis Based on the Probability of Undetected Appendiceal Perforation**

(The title has been changed according to the reviewer's suggestion)

**Authors: Sang Chul Lee, Geon Park, Byung-Jo Choi, Say-June Kim**

**Name of Journal:** *World Journal of Gastroenterology*

**ESPS Manuscript NO:** 11985

**The manuscript has been improved according to the suggestions of reviewers:**

**1 The format has been updated.**

**2 Revisions have been made according to the suggestions of the reviewer.**

## COMMENTS TO AUTHORS AND AUTHOER'S RESPONSES

This is a retrospective study that tries to identify risk factors for in-hospital perforation in patients with acute non-perforated appendicitis previously assumed by CT. Four factors were identified as predictors for gross perforation. The most important surgical implication is the establishment of surgical priorities based in the classification of the patient in a low, moderate or high risk group.

This is a very good paper, well-designed and correctly presented, with no major language problems.

**Strengths:**

-A very rigorous design, absolutely correct. When referring to the design, the clarity of the inclusion criteria, the algorithm of inclusion, definitions and terminology, operative procedures and perioperative treatment are particularly remarkable.

-Results calculations and presentation: tables are clear and appropriate. We will suggest later how to deal with the figures.

**Suggestions:**

-The most important one is the central philosophy of the paper: authors assume that all the selected patients really have acute non-perforated appendicitis as they arrive to the hospital, based on the CT-findings, and that perforation occurs in-hospital meanwhile the patient is waiting for surgery. As the authors explain in their paper (introduction and discussion), this is not considered so in most recent hypothesis over the etiology of acute appendicitis (AA). Most authors agree that AA may develop as non-perforated or perforated since the beginning of the clinical course, and what really happens is that CT may not identify clearly the whole patients that present with perforated forms of the disease. This may be seen clearly for example in the paper from Vons et al (Vons C, Barry C, Maitre S, Pautrat K, Leconte M, Costaglioli B, Karoui M, Alves A, Dousset B, Valleur P, Falissard B, Franco D. Amoxicillin plus clavulanic acid versus appendicectomy for treatment of acute uncomplicated appendicitis: an open-label, non-inferiority, randomized controlled trial. Lancet 2011; 377: 1573-1579), where an unexpected perforation rate of 18% was found even with the systematic use of CT as diagnostic criteria. The authors of the paper that we're reviewing also cite a reference about the low sensitivity and specificity of CT in predicting appendiceal perforation (reference 22: Fraser JD, J Pediatr Surg 2010), which reinforce what we're talking about.

Unfortunately, this affects the globality of the paper, and a substantial change in introduction and discussion is strongly suggested from this reviewer. Sincerely, I think that authors have performed a good statistical analysis and approximation to identify risk factors of perforation, but these factors must be used as the way to identify patients with perforated forms of the disease even when CT doesn't suggest this (and then, as the authors purpose, establish surgical emergencies avoiding septic complications during postoperative course) rather than assume that when these factors are present in a non-perforated form (established as this by CT) the probability of in-hospital perforation is higher.

**RESPONSE:** We have given a lot of thought to your proposal, and have also reviewed the relevant literature. The authors concluded that your opinion—changing the central philosophy—is very reasonable, and the adoption of your suggestion would improve the value of this paper. Therefore, we have changed the central philosophy of this paper. We have extensively revised the paper, especially the introduction and discussion sections. To avoid confusion, we used the terms “in-hospital perforation” or “gross perforation” less frequently. The title of this paper was also changed from “A Novel Strategy for the Determination of Surgical Priorities in Appendicitis Based on the Probability of In-hospital Gross Perforation” to “A Novel Strategy for the Determination of Surgical Priorities in Appendicitis Based on the Probability of Undetected Appendiceal Perforation.”

-I would purpose other suggestions to improve the quality of such a good manuscript, always under the humble opinion of this external reviewer:

\*Abstract: Very clear and resumed. But when the four risk factors related with perforation are cited, there is one that is different in the abstract and discussion and later in the results: in the abstract and the discussion, out-of-hospital symptom duration  $\geq 7$  days is described as one of the risk factors but in results this criteria is substituted by out-of-hospital delay  $\geq 72$  hours. This must be cleared by the authors and expressed as the same criteria along the paper.

**RESPONSE:** We sincerely apologize for this oversight. The correct datum is “72 hours,” not “7 days.” We have made the necessary rectifications throughout the paper. Thank you for bringing this to our notice.

\*Introduction: as expressed above, I would suggest major changes in the introduction based on the current hypothesis of acute appendicitis.

**RESPONSE:** According to your recommendations, we have made major changes to the introduction based on the current hypothesis of acute appendicitis. Thank you.

\*Materials and Methods: Study Design and Data Collection, and Definitions and Terminology are absolutely clear and don't need any changes. Only a few papers offer such a high quality in these aspects.

Operative technique is well described. According to authors' description, open technique has been selected based on the severity of the disease. However, this is not translated later in the results: in table 4, only 6 patients (of 1236) have been operated by open surgery, but the majority of them (5) had no gross perforation found during surgery. I strongly suggest that these 6 patients were excluded of the analysis, as they don't represent a significant proportion and the information rescued from them is not consistent.

**RESPONSE: Thank you for raising such an important point. We incorrectly described the indication of open appendectomy. Therefore, we deleted the related sentences. We think that your suggestion of excluding the 6 patients with open appendectomy from the analysis is very reasonable. However, excluding these patients would represent a complete re-analysis after adjusting the inclusion criteria. Therefore, we humbly ask the reviewer to allow the analysis as is, if the reviewer considers that the inclusion of these six patients will not affect the conclusion. We apologize for our request. The following sentences are the revised descriptions for operative method.**

**“The initial series of this study included patients who had undergone open appendectomy. Soon after, laparoscopic appendectomy with three ports became the norm in the treatment of acute appendicitis. Thereafter, we introduced the single-port laparoscopic surgery (SPLS) for appendectomy in March 2009. Since then, the SPLS replaced the conventional 3-port procedure.”**

The initial series of this study included patients who had undergone open appendectomy. Soon after, laparoscopic appendectomy with three ports has become the norm in the treatment of acute appendicitis. In March 2009, we introduced the single-port laparoscopic surgery (SPLS) for appendectomy, and since then, the SPLS replaced the conventional 3-port procedure.

Regarding perioperative treatment, I would comment the following:

.Second generation cephalosporins are no longer used as prophylaxis or treatment for acute appendicitis.

**RESPONSE:** Regrettably, we did not recognize the transition of antibiotics usage. According to your opinion, we are planning to reorganize our protocol for perioperative antibiotic administration. Thank you for bringing this to our notice. We have rewritten the passage on perioperative management as follows:

“We implemented a standardized perioperative protocol. For all patients with appendicitis, the initial step at the emergency department includes prompt intravenous hydration using crystalloid fluids and intravenous antibiotics (cefotetan 1.0 g). Because cefotetan is administered according to a 24-hour dosing schedule, it was administered at the emergency department and not at a specific time before the incision. Thereafter, starting on the first postoperative day, intravenous cefotetan (usually 1.0 g, maximum dose 2.0 g) was usually administered for 1 to 2 days, or longer if needed. All patients with appendiceal perforation received intravenous metronidazole 50 mg/kg coadministration (maximum dose 2 g). Antibiotic change or dosage adjustments were considered when there was no improvement of the clinical parameters, such as body temperature or leukocyte count. All Patients were allowed a clear liquid diet upon returning to the ward, and the diet was advanced as tolerated. Patients received intravenous ketorolac 0.1 mg/kg as needed for pain. Patients were discharged when tolerating a regular diet. At discharge, oral antibiotics (cefaclor or cefcapene) were prescribed for a 3-day period only to the patients with perforated appendicitis.”

.The significance of  $\geq 1$  appendiceal perforation as a reason to modify postoperative treatment is unclear (explanation, reference...).

**RESPONSE:** This was an error. We apologize for the mistake, and we have deleted the sentence from the revised version.

.Concerning postoperative change of antibiotics, perhaps the evaluation of reactive C protein as a sign of infection control would have been better than the measurement of white cell or body temperature alone.

**RESPONSE:** Excellent comment. We will use CRP for adjustment of antibiotic treatment hereafter. Thank you.

\*Results:

.Changes must be taken into account for the author's institution as it is really surprising that some patients have to wait until 3 days to undergo an appendectomy.

**RESPONSE: Our principle is prompt appendectomy.**

**There were 14 patients whose times-to-incision were  $\geq 48$  hours; 9 patients were 48 - 60 hrs, and 5 patients were 60-72hr. The reasons for the different times elapsed in each case were the diagnostic uncertainty (n = 8), patient's refusal to undergo operation owing to several causes (n = 3), and the changes in the therapeutic plan (n = 3).**

.Concerning median time to incision, it is expressed in the chapter of results that is has been 372.5 min, but in figure 3 it is expressed that is has been 521 min (I think it's the median time to incision for in-hospital gross perforation group). Perhaps it has been a question of mean or median, but in both sides there are different values and the authors refer to it as the same (median). It must be cleared.

**RESPONSE: The authors greatly apologize for the confusion. We miswrote the number in Figure 3. The mean time-to-incision of 373 min is correct. We have corrected the number in Figure 3. We appreciate your detailed revision.**

.When referring to p values, they must all be expressed as  $p \leq \dots$ , never  $p = \dots$ . And I think it's a good practice not to refer all the not significant p values (it is better to refer them as not significant, n.s.).

**RESPONSE: Thank you for your kind observation. The *P*-values have been changed as suggested.**

.Page 7, line 10: Textually: “Both groups were similar with respect to sex, body mass index, comorbidity, out-of-hospital delay, and time to incision. We were also unable to identify a significant difference in time to incision (534 (no gross perforation group) vs 521 (in-hospital gross perforation group))”. Two things must be cleared here:

-First, that it’s the same thing told twice (referring to time to incision).

-And second, that it’s surprising that the global median is 372 but mean in groups have been 534 and 521. One may think that is has been because a little number of patients has been operated with a long delay and this has pulled the mean to the right, clearly influenced by extreme values. Perhaps this needs an explanation for readers.

**RESPONSE: We have deleted the duplicated description. Additionally, you have pointed out very well the reason for the difference between the mean and median values of the time-to-incision. We added the explanation for the difference as follows.**

**“There were differences between the mean and median values of time-to-incision to some extent. While the mean time-to-incision was  $534 \pm 498$  min, the median time-to-incision was 373 (48–4285) min. These results could be attributed to the small number of patients who were operated with a long delay, which translated into a deviation of the mean values to the right.”**

.I don’t see the clear necessity of figure 2, and I would avoid the paragraph related with this figure. Tables are better and essential for this paper, and I suggest that with 5 tables and 2 figures is enough for this paper. I would also think about joining tables 2 and 3.

**RESPONSE: Thank you for the suggestion. The manuscript text has been changed as suggested; figure 2 was deleted (related paragraph was also deleted), and table 2 and 3 were joined. Thank you.**

.In Identification of factors affecting in-hospital appendiceal perforation, the question of which factor has been detected (< or >72 hours of out-of-hospital delay or < or > 7 days of out-of-hospital symptoms duration) must be cleared again. The score constructed with the factors

that the authors identified by logistic regression is the strongest part of the paper, and I think it's particularly interesting.

**RESPONSE: We apologize for the oversight. The correct datum is "72 hours," instead of "7 days." We have corrected this error throughout the paper. Thank you.**

.In Assessment of the influence of in-hospital appendiceal perforation:

-The difference in complications rate is not only notorious in Clavien's grade III as the authors purpose. Grade I and Grade II show clear differences between groups: in grade I, 5 (0.8%) vs 0 (0%) gives a  $p < 0.000$ , not  $< 1$ . And in grade II, considering that a  $p$  value of 0.051 is not statistically significant supposes that we work as slaves of a predetermined value of 0.05.

**RESPONSE: We concluded that there was no difference in grade 1 complication because the  $P$ -value was 1.000. The reason for the lack of difference in the values (0.8% vs. 0.0%) was possibly the considerable difference in the number of patients in each group (1146 vs 90). We are in line with your opinion regarding the grade 2 complication. The manuscript has been changed as follows.**

**"We then classified postoperative complications according to Clavien's proposal (Table 4). The actual perforation group had higher incidence of grade 2 (14.4% vs. 8.2%,  $P = 0.051$ ), grade 3 (7.8% vs. 1.2%,  $P < 0.001$ ), and total number of complications (22.2% vs. 9.9%,  $P < 0.05$ ). The difference in the complication rates was more marked for grade 3 complications. Grade 3 complications were observed in 1.2% of patients in the control group and 7.8% in the actual perforation group."**

-It is surprising too that all the Clavien's III complications have needed reoperation: especially for intraabdominal abscesses, percutaneous drainage if  $> 5$  cm or antibiotic treatment alone for  $< 5$  cm are usually enough as treatment option, and only those without window for percutaneous access must be considered for surgical drainage. I think that the authors must clarify this.



**RESPONSE:** We reviewed 14 cases of intraabdominal abscess, in which patients underwent surgical intervention ultimately. We agree that radiological intervention might have improved the conditions of some of these patients. We think that our preference for rapid and definitive improvement has resulted in the higher incidence of surgical interventions. We promise to abide by the principles of coping with the complications through further management hereafter. We have added the following sentence in the method section.

**“All grade 3 complications in both groups resulted in reoperation, possibly owing to our propensity to adopt a more rapid and definitive management.”**

-Even when it can be supposed, a very quick reference to zero mortality must be performed.

\*Discussion: following with what was expressed before, I would suggest a reorientation of the whole discussion. As authors recognize among the limitations of the study, it cannot be verified “that the study population excluded patients with gross perforation at initial presentation completely...”. Unfortunately I disagree with authors in the affirmation that follows their argument, “... although we thought the possibility was extremely low”. Looking for literature about the predictive capacity of CT of detecting perforated forms of the disease, I think that this probability is high and this is the most important question that affects the central philosophy of this paper.

**RESPONSE:** Thank you for the appropriate comment. We recognize the point well—the central philosophy—as you have mentioned. A considerable number of paragraphs have been changed in the discussion section according to this point. Most parts of the “study limitation” statement were related with our previous philosophy. Therefore, we chose to delete the “study limitation” statement.

I would ask too for an explanation of the following affirmation given in the discussion: “appendectomy is much less urgent in cases of perforated appendicitis”.

**RESPONSE:** It is imperative to perform appendectomy prior the development of appendiceal perforation, because gross intraperitoneal contamination occurs after the

**perforation. Therefore, we think immediate perforation is more of an emergency than perforated appendicitis. The cited sentence—appendectomy is much less urgent in cases of perforated appendicitis—was used in that context. Nevertheless, this statement is not mentioned in the current paper, which has undergone extensive revisions.**

#### **SUMMARY**

This is a good paper, with a very good and rigorous design, with clear definitions of variables and interesting information obtained from an absolutely correct statistical analysis, bi and multivariate. Leaving apart minor corrections that may be easily remedied, it is born from a weak hypothesis and perhaps it must be otherwise designed and conceived. Information obtained from this design must be utilized as it is really interesting, and only a few reports have given such a good approximation to risk factors of perforated appendicitis in the presence of a normal CT.

#### **3 References and typesetting were corrected**

**The authors sincerely honor the excellency and kindness of the reviewer and the rapid progression progression through peer review. This is the reason why we highly value the World Journal of Gastroenterology. We really appreciate the reviewer for the efforts and time put into this review as it has helped us to improve this paper. Thank you again for giving us the opportunity to publish our manuscript in the World Journal of Gastroenterology.**

**Sincerely yours,**

A handwritten signature in grey ink, appearing to read 'Kim SJ' with a stylized flourish at the end.

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