

ESPS Peer-review Report

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Title: A Novel Strategy for the Determination of Surgical Priorities in Appendicitis Based on the Probability of In-hospital Gross Perforation

Reviewer code: 02911182

Science editor: Yuan Qi

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CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
<input type="checkbox"/> Grade A (Excellent)	<input type="checkbox"/> Grade A: Priority Publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B (Very good)	<input checked="" type="checkbox"/> Grade B: minor language polishing	<input type="checkbox"/> Existed	<input type="checkbox"/> High priority for publication
<input checked="" type="checkbox"/> Grade C (Good)	<input type="checkbox"/> Grade C: a great deal of language polishing	<input type="checkbox"/> No records	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D (Fair)	<input type="checkbox"/> Grade D: rejected	<input type="checkbox"/> Existed	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E (Poor)		<input type="checkbox"/> No records	<input checked="" type="checkbox"/> Major revision

COMMENTS TO AUTHORS

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.

-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 ≥ 7 days is described as one of the risk factors but in results this criteria is substituted by out-of-hospital delay ≥ 72 hours. This must be cleared by the authors and expressed as the same criteria along the paper.

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

*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.

Regarding perioperative treatment, I would comment the following:

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

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

.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.

*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.

.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.

.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.).

.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.

.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.

.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.

.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.

-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



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access must be considered for surgical drainage. I think that the authors must clarify this.

-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.

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".

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.