Author’s response to reviews

Title: Acute abdominal pain: concomitant leukocytosis and lymphopenia predict significant pathology on CT. A case-control study

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Version: 1 Date: 19 Dec 2018

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MS: EMMD-D-18-00099

“Acute abdominal pain: concomitant leukocytosis and lymphopenia predict significant pathology on CT. A case-control study”

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Answer to Editor’s and Reviewers’ comments

Dear Editor,

Please find attached the revised version of our manuscript “Acute abdominal pain: concomitant leukocytosis and lymphopenia predict significant pathology on CT. A case-control study”

Changes are highlighted in red in the revised text of the manuscript
Editor Comments:

General:

1. This is a very interesting study asking an important question – how to reduce the ordering of unnecessary CTs. However, I think the outcome of interest is not the optimal one from an emergency physician standpoint. What we want to know is when we can avoid the use of CT – i.e. what predicts a negative CT (instead of the current study which asks what predicts a positive one). With all the data being collected, it seems that a re-analysis would be possible, focused on this clinically relevant question.

Answer to Editor’s general comments:

The answer to Editor’s general comments concerning the outcome of interest is reported below, in the point by point answers (abstract, introduction and discussion).

Abstract:

1. Methods should start with a simple description like “this was a retrospective cohort study of patients presenting to the ED with …” There should also be a short description of the setting – single center academic (?) ED with an annual census of 60,000 patient visits. A brief description of eligibility criteria should also be mentioned. Also mention the years of the study.

2. The variables extracted from the EHR are good, but there should also be a description of who did the extraction (how many people, level of training, inter-rater reliability calculated, etc).

Answer to Editor’s comments #1 and # 2

We have added the requested information in the abstract, as follows:

“This was a retrospective cohort study performed in the emergency department of an academic center with an annual census of 60’000 patients. 109 consecutive patients presenting with an acute non-traumatic abdominal pain, not suspected of appendicitis or renal colic, during the first semester of 2013, who underwent an abdominal CT were included.

Two medical students, completing their last year of medical school, extracted the data from patients’ electronic health record. Ambiguities in the formulations of clinical symptoms and signs in the patients’ records were solved by consulting a board certified emergency physician. Nine clinical and biological variables were extracted: shock index, peritonism, abnormal bowel sounds, fever (>38°C), intensity and duration of the pain, leukocytosis (white blood cell count >11G/L), relative lymphopenia (<15% of total leukocytes), and C-reactive Protein (CRP). These variables were compared to the CT results (reference standard) to determine their ability to predict a significant pathology”.

With regard to Editor’s general comments, we have also modified the Background and Conclusions sections of the Abstract, as follows:

“Background

Acute abdominal pain accounts for about 10% of emergency department visits and has progressively become the primary indication for CT scanning in most centers. The goal of our study is to identify biological or clinical variables able to predict or rule out significant pathology (conditions requiring urgent medical or surgical treatment) on abdominal CT in patients presenting to an emergency department with acute abdominal pain. “

“Conclusion

The high specificity of the association between leukocytosis and relative lymphopenia amongst the study population suggests that these parameters would be sufficient to justify an emergency CT. However, none of the parameters could be used to rule out a significant pathology. “

Intro:

1. References 9 & 10 are not guidelines and should be removed from the sentence as currently written or revise the sentence to more accurately reflect that these are studies (by this research group) that support the recommended guidelines.

   Answer: As suggested by the editor, we have removed References 9 and 10 from the sentence.

2. Avoid using the term “emergency room” and replace with “emergency department.” Emergency physicians are annoyed by the “ER” term since it’s viewed as condescending and doesn’t reflect the nature of our work (clearly we work in more than one room).

   Answer: We have replaced the term “emergency room” with “emergency department” in the manuscript.

3. As mentioned in my general comments, this paper would be substantially strengthened if instead of trying to develop a model to predict when the CT would be positive, it developed a model to predict when it would be negative. I know this may sound semantic, but the point of clinical decision rules is to help decide when CT is not needed, not to maximize the yield of CT.

   Answer
As suggested, we have modified the goal of our study as follows:

“This study sought to analyze whether an association between clinical and biological variables, among examinations routinely performed on patients presenting with not well defined acute abdominal pain, could predict or rule out the presence of a significant intra-abdominal condition on CT, namely one requiring urgent medical or surgical treatment”.

We have also removed the last sentence from the goal of our study:

“[If so, such association could justify immediate CT scanning, thus shortening the triage process of these patients.]”

Also, we have modified the first paragraph of the discussion part as follows:

“The aim of our study was to determine which of the clinical and laboratory variables obtained at patients’ admission to an emergency department were predictive of the presence of significant pathology on CT. Our results show that the only variables meaningfully associated with the presence of a significant pathology on CT are leukocytosis and relative lymphopenia, and that the joint presence of these two anomalies may warrant an abdominal CT on its own merit. However, none of the parameters could be used to rule out a significant pathology”.

Methods:

1. Please add subheadings in the methods section (usually design and setting, patient selection, data abstraction protocol, data analysis, etc). This helps to break up the text and makes it easier for readers to find their information.

Answer: As suggested, we have added subheadings in the Method section.

2. When the phrase “admitted” is used in this manuscript, I imagine the intent is to convey that they “presented” to an ED. This can be confusing for readers in the U.S. since an admission here means going to a ward of the hospital (the ED is considered an outpatient setting here, despite being in the hospital).

Answer: As suggested, we have replaced “admitted” with “presented”.

3. Reading through the eligibility criteria, it seems that the point was to select patients who had abdominal pain that wasn’t well defined (i.e. – not appendicitis or renal colic). If correct, it would be helpful to mention that in the objective of the study.
Answer: we did so

“This study sought to analyze whether an association between clinical and biological variables, among examinations routinely performed on patients presenting with not well defined acute abdominal pain, could predict or rule out the presence of a significant intra-abdominal condition on CT, namely one requiring urgent medical or surgical treatment”.

4. It’s not clear why a period of 20 weeks was selected for the eligibility period. Please elaborate since this is unconventional (usually 6 months or a year).

Answer:

We have matched the duration of the study with the length of the emergency physicians’ rotation, in order to follow the activity of a same team during the survey. In our emergency department, physicians work on a basis of a 6 month rotation period, with an overlap between teams during the last four weeks of rotation. This explains why the study period was 20 rather than 24 weeks. We have mentioned this point in the text:

“The study population was identified by means of an electronic search of the radiology department database, using the keywords “acute abdominal pain”, among all patients referred for CT in the emergency department across a period of 20 weeks, which corresponds to the rotation duration of a single team of emergency physicians in our center, without overlap with other teams.”

5. The data abstraction methods are not well described. Please adopt the recommendations from Kaji et al 2014 Academic Emergency Medicine – Looking through the retrospectoroscope. This will make things much clearer to your readers and highlights any potential sources of bias.

Answer: We have mentioned in the text how and by whom the data were collected, as follows:

“The study population was identified by two medical students (CF, LM), completing their last year of medical school, under supervision of a board certified radiologist, by electronic search…”

“This extraction was performed by the same medical students who already identified the study population. Ambiguities in the formulations of clinical symptoms and signs in the patients’ records were solved by consulting a board certified emergency physician (OTR). The extracted parameters are listed below (the thresholds for abnormality are indicated in parenthesis)”:

6. Regarding your reference standard, who made the determination of “significant pathology?” Was there one person or a panel? Was there definitions created before the study began? Please describe in detail.
Answer:

We did clarify in the text:

« A significant pathology was defined prior to the beginning of the data collection in consensus by the attending physicians representing the units of emergency medicine (AHP, OTR), emergency surgery (EA) and emergency radiology (AP, PAP), as a condition which explained the abdominal pain and required medical or surgical treatment. »

Results:

1. Please give inter-quartile ranges for means, in addition to the already presented ranges.

Answer:

As suggested, we have added the inter-quartile ranges in the text. We have also corrected a typo which occurred when reporting patients’ age.

“Our study population consisted of 109 patients, 60 women and 49 men, with a mean age of 59 years (range 16-94, inter-quartile range (IQR) 46-78). There were 71 (65%) positive CT examinations. The group of patients with a positive CT was made up of 38 (54%) women and 33 (46%) men, with a mean age of 57 (range 16-93, IQR 41-77). The group of patients with a negative CT was made up of 22 (58%) women and 16 (42%) men, with a mean age of 62 years (range 20-94, IQR 50-79)”.

2. When you present the number and percent positive, it is unusual to also include the number and percent negative (it’s simple subtraction from the total).

Answer

We have removed from the text the number and percentage of negative CTs.

In Table 2, it was necessary to indicate the negative number and percent, because of the missing data. Removing the negative CT and just indicating the total number of patients evaluated for each parameter would make the table more difficult to understand. For clarity, we have also added the number of missing data in the table, to comply with your request #4.

3. Is it standard practice to order a lipase for evaluation of pancreatitis or a urinalysis for evaluation of pyelonephritis in patients with abdominal pain? It seems a bit unusual to have these diagnoses made by CT.

Answer:
We do agree with these observations. Actually, in our institution, lipase and urine analysis are not systematically performed in every patient admitted with acute abdominal pain. Thus, the diagnoses for the 4 patients with pyelonephritis and the 6 with pancreatitis were not suspected prior to CT. We have added this information in the text:

“One case of appendicitis, one case of renal colic, 4 cases of pyelonephritis and 6 cases of pancreatitis were identified on CT; these diagnoses had not been suspected before the CT scan was ordered.”

4. How were missing data handled? How much data were missing? Was imputation used? If so, what type?

Answer:

No imputation was used and only non-missing data were analyzed.

We have added this information in the text, as follows:

“Only non-missing data was analyzed”.

For clarity, missing data were added in Table 2.

5. The number of paragraphs in the results should be condensed. Right now, it reads as if there are 5 bullet points that were turned into 1-2 sentence paragraphs.

Answer:

As suggested, we have reduced the number of paragraphs in the result section.

Discussion:

1. Overall well written and nicely places the results of the study in the context of the literature at large. If anything, it may be a bit long and could benefit from some streamlining of content.

Answer

If possible, we would prefer not to modify the discussion part, which could reduce the clarity of the explanations.

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system. We encourage you to also view the reports there, via the action links on the left-hand side of the page, to see the names of the reviewers.

Reviewer reports:

Alireza Baratloo (Reviewer 1):

Question 1:
- I suggest you to calculate "r" to report the exact correlation between your measured variables with positive findings in CT scan.

Answer to Reviewer 1, Question 1

According to our statistician, the relationship between categorical variables is evaluated by groups' comparison (Chi-square test), not by correlation. The correlation analysis is better suited to exploring relationships between continuous variables, which was not the case in our analysis.

In our study, for each laboratory parameter, the threshold for abnormality was determined prior to CT, based on what is considered normal and abnormal values in our institution.

Question 2:
- Reporting p-value is not as valuable as reporting an odds ratio in the abstract.

Answer to Reviewer 1, Question 2

We do agree with this observation and have reported the Odd Radio instead of the p value in the abstract:

“Only leukocytosis (odds ratio 3.3, p=0.008) and relative lymphopenia (odds ratio 3.8, p =0.002) were associated with significant pathology on CT”.

Michael Ward, M.D. (Reviewer 2): Well-written and does correctly identify significant limitations.

The scope of the study does not justify the conclusion. As noted in the limitations, this study only evaluates patients in which a CT was obtained and does not assess all comers for abdominal pain. Therefore, suggesting that the combination of leukocytosis and lymphopenia by itself "would be sufficient to justify emergency CT" seems presumptive. Additionally, odd there is a significant degree of missing data for markers that would seem to be readily available for a
retrospective study. I also reject the claim that many of the CT findings provide a benefit to the patients being scanned. Several of the diagnoses have traditionally fit into that of a clinical diagnosis which often does not require imaging.

Answer to Reviewer 2

Actually, the scope of the study was also to determine criteria that can predict a negative CT, which could be useful to reduce the number of CTs; we have found none. As suggested by the Editor, we have added this observation in the text. Of course, the study was focused on a population of patients for whom a CT has already been prescribed by the emergency physician, without information about those patients who were examined and treated without CT. The aim of the study was not to evaluate the triage of the acute abdominal pain patients to CT, but just to determine criteria that could definitively obviate the need of performing a CT after the decision has been reached by the clinician to obtain this CT. In spite of the missing data, our analysis showed that no clinical or laboratory criteria were sufficient to rule out a significant pathology at CT in this specific population. The same conclusion would have been reached if all data were available. We don’t completely agree with the last sentence of Reviewer 2. Indeed, a study from the MGH showed that the leading diagnosis of the clinicians in emergency situation changed after CT in 51% of patients with acute abdominal pain (Pandharipande PV et al., Radiology, 2016).