Author's response to reviews

Title: A Prospective Cohort Study of Postoperative Complications in the Management of Perforated Peptic Ulcer

Authors:

  Smita S Sharma (smitassharma@yahoo.co.uk)
  Manju R Mamtani (manjumamtani@rediffmail.com)
  Mamta S Sharma (mamtassharma@rediffmail.com)
  Hemant Kulkarni (hemant_kulkarnius@yahoo.com)

Version: 2 Date: 26 May 2006

Author's response to reviews: see over
May 25, 2006

To,

The Editor,
BMC Surgery.

Re: MS: 1277303691939868 - A Prospective Cohort Study of Postoperative Complications in the Management of Perforated Peptic Ulcer.

Dear Sir/Madam,

First of all, we would like to thank the BMC Editorial Team and the three reviewers for a very detailed and encouraging review of our abovementioned manuscript. We have revised our manuscript based on the suggestions of all the reviewers and herewith submit it for a favorable consideration for publication in BMC Surgery.

Following is our point-by-point response to all the concerns expressed by all the reviewers. We have also indicated in our response where the changes have been made in the revised manuscript. Further, we have formatted the documents as suggested in the Instructions for Authors and have updated the figures in a format compatible with the instructions provided on the website of BMC Surgery.

Again, we thank you and the reviewers.

Sincerely,

Hemant Kulkarni, MD
Reviewer #1

Point #1:

Reviewer’s comment:
“Regarding the analysis, the censored event is the development of a complication. However, this single censored event, in fact, comprised a heterogeneous groups of complications. This jeopardized the validity and applicability of the results.”

Our Response:
We agree with the Reviewer that the manner in which the censored event has been defined in our study can potentially make the interpretations and inferences challenging to draw. In somewhat different words, Reviewer #3 also appeared to share this concern. Here, we provide our point-of-view on this important issue which, we think, only minimally influences the interpretations of this study.

Precedence:
- A conglomerate outcome is very commonly employed in epidemiological studies. Following is a list of some recent studies that have also used a similar analytical approach to combine the complications:
- In many ways, our definition of a complication is similar to an end-point like AIDS which is a conglomerate of several AIDS-defining illnesses and is quite commonly used in cohort studies dealing with that disease. (e.g. Gonzalez E et al, Science 2005) Another example would be the use of “all cause” mortality which is used in innumerable studies as an endpoint. (e.g. Kangasniemi et al, 2006)
- Indeed, even in the literature related to postoperative mortality in perforated peptic ulcer, most of the studies combine all causes of mortality into a single variable. Further, Makela et al, 2002 have also combined the postoperative morbidity of all types into a single composite dubbed as “postoperative morbidity”. Considering all these instances from published literature, we think that precedence existed for us to be able to define a composite outcome variable.
Clinical Rationale:
As correctly pointed out by Reviewer #3, the focus relating to postoperative assessment in perforated peptic ulcer now needs to shift from mortality to morbidity. In that case, we think that clinicians will be immensely benefited by knowledge of the factors that can predict all types of complications rather than a specific complication. Further, since all the subjects recruited in our study represented a comparably late presentation of the perforated peptic ulcer and most of the patients received the same type of treatment, the postoperative complications (all included into a single variable) represent an overall starting point for the association-type of analyses in our study.

Statistical Rationale:
In the interest of a more methodologically sound and clinically meaningful analysis as suggested by the Reviewer, it would have been beneficial to conduct either separate analyses using each type of complication as a separate outcome variable or (as indicated by Reviewer #3) employ multivariate methods like multivariate Cox regression analyses (e.g. Genser B and Wernicke KD, Biom J, 2005), Generalized Estimating Equations (e.g. Shelton et al, Comput Methods Programs Biomed. 2004) or Structural Equations Modeling (SEM). However, since the number of subjects with each specific type of complication observed in our study was not large, the use of multivariate analytical approaches was restricted for the want of adequate statistical power. The conglomerate variable of “postoperative complication” partially circumvents this problem.

Considered together, we believe that our analytical approach was suited to the dataset being analyzed. We have thus, in the revised version, persisted with the conglomerate outcome. We agree with the Reviewer that for datasets with large number of subjects with postoperative complications, it will be more informative to conduct subgroup or multivariate analyses. Since this was an important limitation of the study which was not mentioned in the previous draft, we have now included it in the Discussion section on page 15. We thank the Reviewer immensely for bringing out this caveat.

Point #2:
Reviewer’s Comment:
“Besides, it is difficult to determine the commencement time of the censored event. Frequently, complication started soon after operation.”

Our Response:
We thank the reviewer for pointing out this deficiency in presentation. We have now included information on the median time to complications in panels A through E of Figure 2. We have also updated the legends to Figure 2 accordingly.

Point #3:
Reviewer’s Comment:
“Instead of focusing on the rate of developing complication or risk of developing no. of complications, most readers are more concerned about complications requiring surgical intervention and ultimate outcomes of the patients. Authors should point the clinical relevance or importance of evaluating the rate of developing complications and the no. of complications. Types & no. of surgical intervention, as well as causes of death should be given.”

**Our Response:**
We thank the Reviewer very much for this valuable suggestion. As explained in our response to Point #4 (please see below), we have now included a paragraph in the Results section (page 11) specifically addressing the surgical relevance of the postoperative complications observed in the present study. We have also provided more description of the causes of death (page 10).

**Point #4:**

**Reviewer’s Comment:**
Did the rate of developing complication and higher no. of complications influence the mortality?

**Our response:**
We are indebted to the Reviewer for asking this question, which prompted us to do more analyses as well as to address the previous question about the relevance of our study outcomes. As explained in the Discussion section (page 13), we have now addressed this issue.

**Point #5:**

**Reviewer’s Comment:**
“What was the blood group selected to be a predictor?”

**Our Response:**
In the multivariate analyses, we included all the blood groups to as predictors. The reference used was the commonest blood group (ORh^+).

**Point #6:**

**Reviewer’s Comment:**
“Please define abdominal distension. Any objective criteria? 39% of patients had abd. Distension appeared unusual.”

**Our Response:**
For the purposes of our study, we defined abdominal distension as any visible abdominal bloating. However, using a 4-point scale a large Italian study (Maconi et al, 2002) assessed 9,883 dyspeptic subjects with discomfort as the predominant symptom. They found moderate to severe abdominal distension in ~37% of subjects which concurs with
the proportion of subjects with distension observed in our study. Again, we thank the Reviewer for this comment. We have included this point in the Discussion section (page 14).

Point #7:

Reviewer’s Comment:
“Please delete 2nd paragraph on p.9. It appeared irrelevant to the paper.”

Our Response
We have now deleted the paragraph.

Point #8:

Reviewer’s Comment:
“What is 'tension suture'?”

Our Response:
In the text, we have now described this previously ambiguously used term (page 11). We thank the Reviewer for pointing this out.

Point #9:

Reviewer’s Comment:
“In introduction of abstract, objective was not clearly stated.”

Our Response:
We have now clarified the objective.

Point #10:

Reviewer’s Comment:
“Suggest to tabulate features on admission and medical conditions - 1st paragraph of Results.”

Our Response:
Actually all these features have been highlighted in Figure 1E in the form of a bar chart. Since we did not understand whether the Reviewer was suggesting a table in addition to or in lieu of Figure 1E, we have kept Figure 1E as it is.

Point #11:

Reviewer’s Comment:
“Were the 4 subjects without repair really suffering from PPU?”

Our Response:
If we focused on their presentation at the time of admission, they had all the features suggestive of a perforation including gas under diaphragm on X-ray. So, in all probability they had a very small and intra-operatively unnoticeable perforation.
Reviewer #2:

We are extremely grateful to this Reviewer for a highly encouraging review.

Point #1:

Reviewer’s Comment:
“- Data in figure 1E do not correspond to those reported in the manuscript (page 8); “

Our Response:
There were two differences between figure 1E and the text. First, the sequence of variables is different – in text it is in the order of frequency while in the figure it is in groups of the history- and examination-related variables. In the revised version we have persisted with these different ways of presentation of the same data because they highlight the data in different ways. Second, there was no mention of NSAID use in the text. We have now added information on this variable to the text.

Point #2:

Reviewer’s Comment:
“Moreover in the pie chart is shown a slice (marked with an asterisk) whose meaning is not explained.”

Our Response:
We thank this reviewer for pointing out this lacuna. We have corrected it and added the explanation in the legend to Figure 1.

Point #3:

Reviewer’s Comment:
“- Reference n. 19: the correct surname of the fourth author is LISSIDINI G.”

Our Response:
We apologize for this oversight and have corrected the name in the revised version.
Reviewer #3:

Point #1:

Reviewer’s Comment:
Motivation for the presented study is clearly stated and has substantial practical consequences. As authors state in the Background, predictors for morbidity and for mortality might be potentially different and hence those traditional strategies oriented to mortality stratification might not be the best when mortality was (fortunately) lowered and morbidity comes into focus.

Our Response:
We thank the Reviewer for highlighting the implications of our work in such lucid and encouraging words.

Point #2:

Reviewer’s Comment:
Methodologically, the search for a set of good predictors is not entirely easy, nor completely straightforward. The present paper tries to use very standard statistical methodology. Even though various improvements over this “textbook approach” are known, the standard contribution might be useful when presented in appropriate framework, discussed perhaps with a bit of skepticism and mainly in a rigorous way. Especially lack of rigor is what is missing in the paper.

Our Response:
Again we thank the reviewer for supporting our statistical methods in spirit. Based on this Reviewer’s suggestions that follow, we have revised the manuscript in a major way.

Point #3:

Reviewer’s Comment:
Even terminology can be improved a lot to prevent misunderstanding and even misleading conclusions. Typical example of terminological carelessness is repeated use of the notion of “multivariate models” through the text. The techniques that the authors use are all UNIVARIATE. Note that in Statistics (both theory and applications), regression with several explanatory variables is a univariate method (and it is called multiple regression, not multivariate).

Our Response:
We agree with the Reviewer completely and apologize for falling prey to an inaccurate use of the term “multivariate”. All through the revised manuscript, we have now corrected our old use of the term. We thank the Reviewer for helping us bring clarity to the use of words.

Point #4:
Reviewer’s Comment:
There are multivariate generalizations of regression, logistic regression, etc. but they are more complicated (work with several dependent variables at once) and were not used by the authors of this paper at all. True multivariate techniques might be useful in present context (e.g. when considering simultaneous behavior of several complication events), instead of lumping them into more or less artificial composite index dubbed in the paper as “postoperative complication” (note that complications having various causes and consequences are lumped together there in the “apples and oranges” style, so that usefulness of such a measure is a bit questionable from practical point of view).

Our Response:
This comment of the Reviewer overlaps with a similar concern raised by Reviewer #1. We have responded to this (please see our response to Reviewer #1, Point #1).

Point #5:

Reviewer’s Comment:
In any case, statistical models used for the analyses should be clearly stated within the text (as equations showing clearly what is predicted from what). Estimated coefficients should be presented not only in sometimes hard to read graphs, but also in tabular form, point estimates should be accompanied by some quantity expressing uncertainty (e.g. standard errors, confidence intervals, etc.).

Our Response:
We thank the Reviewer for suggesting to include regression equations which we have now included in the Statistical Analysis subsection (pages 7-8). Regarding the results of multivariate regression coefficients, confidence intervals and the p-values, in the original submission these were shown in the Part B of the Additional file. Since a figure based on these coefficients and the coefficients themselves would amount to redundant information, we presented the results graphically in the main text and described these in full details (including which variable was excluded from the stepwise regression and when) in the Additional file (Part B).

Point #6:

Reviewer’s Comments:
Another question of practical interest is generalizability of the results. For instance, the authors stated that the study was conducted in two particular hospitals. Can the spectrum of complications (and their relative frequencies) be expected similar at different places? And are the predictors and their importance similar at different places? These are obviously questions that are hard to answer without further studies, but their relevance should be at least acknowledged in the discussion. Moreover, the fact that the data are available from two locations can be used to perform statistical tests comparing: i) spectrum of complications, ii) predictors between the locations. Obviously, apparent homogeneity between them is only necessary, but not sufficient condition for further
generalizability, but it should be tried as the first attempt. Note that there are many subtleties that can be elegantly studied by means of statistical analysis, e.g. whether the prediction models are about the same for different locations, whether coefficients of the same explanatory variables are similar at different locations, etc.

**Our Response:**
Perhaps the ‘and’ in the name of the institution where the work was carried out led to this connotation of two study centers. Actually, our study was carried out at only one center. Therefore, these extremely interesting comments and suggestions made by the Reviewer do not apply to our dataset.

**Point #7:**

**Reviewer’s Comment:**
Discrepancy between analyses with single explanatory variable and with several explanatory variables taken simultaneously (e.g. that mentioned on page 12) is taken quite lightly, it is not investigated, nor discussed (note that it is by no means automatic that the simultaneous analysis is free of problems remember troubles with collinearity and many others).

**Our Response:**
Actually, we had investigated but not presented the results of correlation analyses among the predictors considering the readership of BMC Surgery. However, we have now added the correlation structure of the dataset in the Additional file (Part C) and have mentioned its meaning in the Results section (page 12).

**Point #8**

**Reviewer’s Comment:**
The way of writing results is too compact sometimes. “(odds ratio, p)” notation is terrible. It would not take too much space to state every time that OR was such and such and p was such and such, while such a provision would enhance readability substantially. “p 0.015” should be replaced by “p=0.015”, etc.

**Our Response:**
We concur with the Reviewer and have rewritten the complete section in an attempt to be “kind to the reader”.

**Point #9:**

**Reviewer’s Comment:**
It is really hard to swallow inherently contradictory statements like “independently predicted” and “independent predictor” that appear within the text. Probably, just the usual “predicted by the explanatory variables considered” is meant but the meaning is masked so that it is hard to decipher.
Our Response:
Again, we have corrected this ambiguous and confusing use of the terms. We thank the Reviewer for the same.

Point #10:

Reviewer’s Comment:
Some variables entering the analyses are not defined previously. For instance, take “history suggestive of shock”. What does it mean precisely? How long history, how was the datum about it obtained. questionnaire/questioning by a particular investigator/taken from routine documentation, etc.?

Our Response:
We have now provided more explanation about this and other variables (page 7).

Point #11:

Reviewer’s Comment:
Graph legend should be much more extensive. For instance, it is not explained what is the meaning of the numbers in Figure 2F (probably p-values, but one has to guess).

Our Response:
We are not sure if the correct version of the Figure legends reached the Reviewer because in our original draft we had explained the meaning of these numbers as well as other details in the figure.