Author's response to reviews

Title: The clinical overlap between functional dyspepsia and irritable bowel syndrome according to Rome III criteria

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Author's response to reviews: see over
Dear Editor,

I am submitting a revised manuscript entitled “The clinical overlap between functional dyspepsia and irritable bowel syndrome according to Rome III criteria (MS ID: 1325076374195375)” for considering publication in BMC gastroenterology.

The paper has been revised in accordance with comments and suggestions made by the reviewers. Modifications are highlighted in red in the revised text and listed on the following pages.

Should there be any further comments on the manuscript, please do not hesitate to contact me.

Thank you for considering our paper for publication in your Journal.

Sincerely,

Minhu Chen, M.D., Ph. D
Reviewer Ami D. Sperber

Major Compulsory Revisions

1. This is a clinic population. This does not provide perspective on the extent of this problem in the general population, which to my mind would be more interesting.

Response:

Yes, this might not exactly reflect the distribution in the general population. But the data from clinic population are more helpful for the pathophysiological studies than those from general population. It is the strength of our study rather than a limitation. As the pathophysiological studies generally enroll subjects from clinic population whose symptom severity and profile are very different from those in the general population, we decided to choose the clinic population.

2. Is it not clear if all the patients are new to the clinic or some are new and others are veteran patients. How many have been treated for IBS or dyspepsia and what effect does the treatment have on the overlap rates?

Response:

Several sentences have been added in the revised version to address this issue (please see page 5, line 10, sentences in red).

All the patients were asked to fill the questionnaire only once. Those who had fulfilled the questionnaires before would not be given the questionnaires again. So patients are all new for this investigation but some were veteran to the clinic.
It was written in the article that all the patients evaluated their symptoms by themselves and those using drugs like NSAIDs, steroids or drugs affecting gastric acid secretion or gastrointestinal motility would be excluded from the diagnosis of FD and IBS. As a matter of fact, the patients who had major psychotic episodes, mental retardation, dementia, severe visual or hearing abnormalities or other illnesses that might render them unable to complete the questionnaire (e.g., stroke) and those using drugs like NSAIDs, steroids or drugs affecting gastric acid secretion or gastrointestinal motility were not included in the consecutive patients.

3. The clinic functions at the primary, secondary and tertiary care level. How were the patients distributed on these lines and did this variable predict overlap? For example, intuitively tertiary care patients would probably have a higher overlap rate.

Response:

We admitted that it is the limitation of our study which was added to the discussion (see page 12, line 15, sentences in red).

Most of hospitals in China are comprehensive. They are open access systems since they provide primary, secondary and tertiary level care. It is similar with our hospital. Patients with any gastrointestinal disorder could seek healthcare in the general gastroenterology outpatient clinic. So patients who should go to the primary, secondary and tertiary care in a large sample should be normally distributed. Our results could reflect the overlap rate in the general gastroenterology outpatient clinic. However, we could make our investigation
only in one hospital. We admitted the patients enrolled were some biased. Our results should be confirmed in a multi-center study in a larger sample in the future.

4. Was chronic co-morbidity assessed? Patients with IBS-FD overlap are more likely to also have other functional co-morbid conditions such as fibromyalgia, CFS, etc.

5. Was somatization assessed and how was it associated with overlap?

Response:

Yes, we agreed with the opinion of the reviewer. We admitted the evaluation of co-morbidity and somatization is also important. However, they were not included in the objective of our study, so we didn’t evaluate them in the present study.

6. The overall rates for IBS and FD seem low considering that this is a specialized clinical population. How do the authors explain these relatively low rates.

Response:

Our perspectives are as follows: 1. In patient-based studies, the rate of concurrence of FD and IBS appears to be between 26% and 46% of FD patients having concomitant IBS [1]. We also conducted an epidemiological study on the FD-IBS overlap in Guangdong general population in 1996[2]. In the general population, the overlap rate was about 4% and 23.7% patients with dyspeptic symptoms suffered from IBS. Our result is similar with these studies. 2. As our hospital provides primary, secondary and tertiary level medical
care, the data from our hospital could only reflect the situation in the general medical clinics rather than a specialized medical center. The rates are possibly higher than those in the general population but perhaps lower than those in tertiary medical care clinics which may fulfill your expectation. The symptom frequency threshold required in Rome III criteria is different from the one in former criteria. According to our former studies [3,4], the prevalence estimates of FD and IBS based on Rome III criteria are much lower than those based on Rome II criteria or Manning criteria.

Our results could be confirmed by other studies in the future. The sentence in Background which said 30%-60% patients with either diagnosis fulfill the other one was not very accurate. In order to make a more accurate description of overlap rate, the figure was changed to 13%-87%. (see page 3, line 3, sentence in red)

Reference

1 Gwee KA, Chua ASB. Functional dyspepsia and irritable bowel syndrome, are they different entities and does it matter? World J Gastroenterol 2006; 12(17): 2708-2712.


The methods section mentions the criteria for the stepwise multiple logistic regression analysis, but there is no mention of it in the results and the tables report only univariate analyses. Was a multivariate model assessed and what were the results?

**Response:**

Several sentences have been changed and added in the Methods and Results in the revised version to address this issue (please see page 7, line 10, sentences in red; page 9, line 8, sentences in red; page 24 Table 3 and page 25 Table 4). In fact, we had made a univariate analysis and omitted the results. We had added the results of univariate analyses to the article. The identification of presence of postprandial fullness as overlap risk factors was assessed by a multivariate model. As the aim of our study was to find the risk factors for overlap of FD and IBS in patients demographics and newly defined symptoms in Rome III criteria, we speculated all these factors were clinically relevant and potential risk factors. We first analyzed these factors with univariate analyses. Then we chose an alpha value of 0.2 to keep potentially important factors in the model as some may become significant just by chance. As our aim was to be control of confounding factor rather than a prediction, we chose a logistic regression and didn’t select them by a stepwise procedure. So our result for risk factors of overlap was changed a little, but the conclusion was not changed.

8. The patients use scales to assess symptom intensity and frequency. It is not clear if these scales were devised specifically for this study or not? If so, how
were they validated before their use in the study?

**Response:**

1. Most of studies used 4 to 7 scale levels to measure the severity of symptoms. It is reported that 5 to 7 point scales have been favored[1]. Considering that an odd number of response options is preferred to allow subjects to select a middle or neutral value, we decided to use 6-point categorical scale. 2. The similar method to evaluate the severity of FD symptoms and abdominal pain or discomfort of IBS was adopted in other studies[2,3]. The reference articles were added to Reference in the revised version (please see page 6, line 10). 3. The classification of frequency of abnormal bowel habit was based on the classification adopted in Rome III IBS questionnaire. The similar 5-point scale was adopted to subclassify IBS patients into different subtypes[4].

Reference


9. There is no limitations section in the discussion. Given that the study has important limitations, many of which are discussed above, the authors need to add this section and discuss why they think these limitations are important and why the results are still valid despite the limitations.

**Response:**

Several sentences have been added in the Discussion to address this issue (see page 12, line 15, sentences in red).

**Minor Essential Revisions**

While the English is reasonably good there are still several grammatical errors and other problems including some matters of nuance. For example, in the “subjects and survey methods” section the authors write: “… two doctors who would not meddle in patients’ medical management.” First the word “would” should be “did”. Second and more important to my mind the word “meddle” is inappropriate and has negative implications. The appropriate word, I believe, is “intervene”.

**Response:**

Yes, a native speaker had been asked to review our manuscript and made some
Reviewer Giorgio Bedogni

Major Compulsory Revisions

1. It is very important that the Chinese versions of the Rome III FD and IBS questionnaires were properly validated. I suppose that this was done in a convenience (possibly consecutive) sample of the study population. Am I right to suppose this? I do not understand however what the ICC refers to (please, give 95% confidence intervals). It is probably a measure of the agreement between the first and the second measure but how did you take into the account the fact that the agreement may differ from one question to another? If this is the first validation of the questionnaire in China, it would be extremely useful to compare the reliability statistics obtained in your population with those obtained in other populations.

Response:

1. The investigation was done in a consecutive sample. However, some patients refused to participate in the study. Some didn’t fulfill the questionnaire completely. Some patients were excluded from the study because of our exclusion criteria. So patients who completed the questionnaires were not consecutive. 2. Yes, We do agree that the validation of Chinese version of Rome III FD and IBS questionnaire is important. We have conducted a research to validate Rome III questionnaire. But we didn’t give detailed information in this study. Test-retest reliability was confirmed by ICC. ICC was enough to
confirm the qualification of this Chinese version of Rome III FD and IBS questionnaire. In another study, The similar method was applied to confirm the reliability of a questionnaire[1]. Yes, we do agree that the ICC of each question in the questionnaire may indeed differ from one to another. However, we use the whole questionnaire to diagnose FD and IBS rather than any specific question. We don’t think it is meaningful to calculate ICCs for every question to ensure the test-retest reliability of the whole questionnaire. Since ICC for the whole questionnaire is 0.88, we think test-retest reliability of Chinese version of Rome III FD and IBS questionnaire is good. This questionnaire is qualified in this investigation. 4. 95% CI for ICC was given in the revised version (see page 6, line3).

Reference


2. You used a 6-point scale to measure the severity of FD symptoms. Was this instrument developed by you? If so, you should give reliability data (see above). If not, you should at least quote other uses in the literature.

3. By summing the severity of all FD symptoms, you are weighing each symptom equally, e.g. a postprandial fullness=5 would equal an epigastric pain=5. I am not sure that this is clinically correct. The relative weighing of symptom severity made by the subject – especially for functional disorders
such as FD and IBS – may differ substantially. Again, are there documented used of a similar 6-point scale in the literature?

P6 The previous considerations apply also to the grading of IBS symptoms.

**Response:**

1. Most of studies used 4 to 7 scale levels to measure the severity of symptoms. It is reported that 5 to 7 point scales have been favored[1]. Considering that an odd number of response options is preferred to allow subjects to select a middle or neutral value, we decided to use 6-point categorical scale. 2. The similar method to evaluate the severity of FD symptoms and abdominal pain or discomfort of IBS was adopted in other studies[2,3].

   The reference articles were added to Reference in the revised version (please see page 6, line 10). 3. The method of summing up the severity of all FD symptoms and IBS symptoms was also adopted in other studies[4,5]. This approach did not disclose a specific symptom pattern for patients with both FD and IBS, but showed that these patients suffer from more severe FD symptoms in general compared to FD alone. It is similar with summing the severity of all IBS abnormal bowel habit. Besides, this method of summing the severity of different symptoms is also widely used in RDQ (reflux disease questionnaire), a questionnaire widely used for diagnosing GERD.

Reference


4. Please, detail clearly the outcome variable and the confounders (or risk factors if you prefer using this latter term as you do in the paper). You say that the OR of having FD and IBS together is 2.09 but I do not understand what is the reference category. I would understand and odds of FD given IBS or vice versa or is this a multinomial odds ? I generally discourage modeling of all interactions as some may be significant just by chance. The choice of interactions to model should be made on the basis of clinical reasoning whenever possible. Whatever the case, the reader can get no picture of the
interactions without having a clearly detailed list of confounders/risk factors. An
alpha value of 0.2 is generally used to keep potentially important confounders
in the model. If this was your idea in using the 0.2 cut-point, I suggest keeping
confounders in the model and not select them using a stepwise procedure.
Your aim does not seem indeed to be prediction but control of confounding.
Please, give the logistic models with control of confounding in Tables.

Response:

Yes. 1. The meaning of odds ratio of having FD and IBS is perhaps not clearly expressed
in Abstract. The sentence in Abstract was revised to address this issue (see page 2, line
11, sentence in red). 2. Yes, I agree with your opinion about logistic regression. The
statistical analysis was revised to address this issue. Although the OR of presence of
postprandial fullness changed a little, the conclusion was not changed after using
above-mentioned statistical analysis method. The sentences in Methods and Results
were revised to address this issue. The tables including all potential risk factors after
univariate analysis were given in Table 3 and Table 4 in the revised version (please see
response above).

5. You performed two univariate 2-group comparison separately but for your
aim is more appropriate to perform a 3-group FD vs. IBS vs. FD+IBS
comparison. Is this perhaps because you have not available all the data for all
groups? Again, this could be better handled by a logistic model with control of
confounding.
Response:

We think it is inappropriate to perform a 3-group comparison. As far as subtype is concerned, none of patients with FD alone could be classified into any IBS subtype because none of them fulfilled IBS diagnosis criteria. It is the similar with patients with IBS alone. We could not perform a 3-group comparison in term of subtype. As far as symptom was concerned, though patients with FD could perhaps have some abnormal bowel habits or patients with IBS could also have some dyspeptic symptoms, these symptoms are not clinic relevant because they don’t have corresponding disorder. They are not clinically relevant. Since most of pathophysiological studies would enroll patients with clinically relevant symptoms and the objective of our study was to provide clues for the pathophysiological study with epidemiological method, It is inappropriate to make a 3-group comparison in term of symptom profile.

MINOR COMMENTS

1It seems that also subjects who refused to participate were given the questionnaire. Why?

Response:

The sentence was revised to address this issue. In fact, we gave questionnaire to patients after they signed the informed consent. However, some patients refused to complete the questionnaire after getting it though they had consented to participate in the survey. In this case, we asked patients to return the uncompleted questionnaire.
2. How were age and sex of non-responders obtained? I suppose from clinical charts. Or from the returned questionnaire?

Response:

In order not to differentiate new and veteran patients, we wrote down their name, sex and the date of visiting doctor no matter whether they decided to participate in our study.

3. How did you plan sample size? On the basis of an expected prevalence, e.g. FD+IBS according to previous studies or on the basis or identification of risk factors?

Response:

Yes, the way of sample size calculation was added to Methods (please see page 4, line 11, sentences in red). We calculated it based on an epidemiological study which was conducted in our province in the general population in 1996 which showed the prevalence of FD-IBS overlap was about 4%.

4. “significant illnesses” is too generic. Please, detail.

Response:

Yes, the sentences were revised to address this issue in Methods (please see page 7, from line 2 to line 5).

5. Give the total number of patients to whom you administered the questionnaire. 3014 responders/0.89 percent makes about 3386 patients.
Response:

Yes, the sentence was revised to address this issue (please see page 7, line 1).