

ANSWERING REVIEWERS

January 25, 2015



Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 15653-Revision.doc).

Title: Relationship Between the Severity of Venous Calcifications and the Symptoms of Phlebosclerotic Colitis

Author: Tsung-Shuo Yen, Chien-An Liu, Nai-Chi Chiu, Yi-You Chiou, Yi-Hong Chou, Chen-Yen Chang

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 15653

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

1 Format has been updated

➔ **Response:** Format of the revised manuscript has been updated.

2 Revision has been made according to the suggestions of the reviewer

Editor in chief

Download the attachment in this e-mail and find the manuscript file edited by the editor in the "Manuscript" column by clicking the link and the title line, with the electronic document title as: ESPS Manuscript NO: 15653-edited. Then please revise your manuscript according to the reviewers' and editor's suggestions, as well as the "Revision Policies of BPG for Retrospective Study (Original Article)". Please note, you will find the editor's suggestions in the edited manuscript file, using the Track

Changes function; these suggestions include formatting-related issues, such as adding authors' affiliations, contributions, and telephone and fax numbers or adjusting the text sections to meet the word count requirements for your article type and target journal.

➔ **Response:** Thank you for your reminders and suggestions. According to the suggestions of electronic document, entitled 'ESPS Manuscript NO: 15653-edited', we revised and added some parts to the revised manuscript. The changes we made as below:

I. All of the revisions you make to the revised manuscript should be cited in the response letter and highlighted in the updated vision, which you downloaded from the ESPS.

➔ **Response:** Thank you for your suggestion. All of the revisions we made to the revised manuscript were cited in this response letter and marked in red in the revision.

II. Please sign and submit all necessary documents, including the **Answering Reviewers response letter and Copyright Assignment form.**

➔ **Response:** Thank you for your comments. Every revision we made was cited in this response letter, which we downloaded from ESPS, and each author signed the Copyright Assignment form.

III. Before uploading the revision, please check the manuscript thoroughly and confirm that all of the references are properly cited.

➔ **Response:** Thank you for your kindly reminder. We checked the revised manuscript thoroughly and confirmed that all of the references were properly cited.

IV. The BPG editorial office will subject the manuscript to *CrossCheck* analysis before its final acceptance. *CrossCheck* powered by *iThenticate* (document checking software) is an initiative started by *CrossRef* to help its members actively engage in efforts to prevent scholarly and professional plagiarism. We suggest that you perform a check of your revised manuscript before resubmission using the *CrossCheck* program.

➔ **Response:** Thank you for your suggestion. We performed a check of the revised manuscript before this resubmission.

V. In order to attract readers to read your full-text article, we request that the first author make an audio file describing your final core tip. This audio file will be published online, along with your article.

➔ **Response:** Thank you for your suggestion. The first author made an audio file according to the specifications to describe our final core tip. Please see the attachment uploaded in the Audio column.

VI. Running title

Please write **a running title** of less than 6 words. See the format in the attachment.

Thank you.

➔ **Response:** Thank you for your comment. We added a running title following the format in the attachment. The change was made and marked in red in the Title page section at page 1, as '*Yen TS et al. Calcifications and Symptoms of*

Phlebosclerotic Colitis.'

VII. Please provide **language certificate letter** by professional English language editing companies (Classification of manuscript language quality evaluation is B). For manuscripts submitted by non-native speakers of English, please provided language certificate by professional English language editing companies mentioned in '**The Revision Policies of BPG for Article**'.

➔ **Response:** We sought a copyediting service provided by professional English language editing companies mentioned in The Revision Policies of BPG for Article and the revised manuscript was edit by **NPG Language Editing**. The language certificate letter was uploaded. Please see the attachment in the **Non-Native Speakers of English** column.

VIII. Please provide **the author contributions**. Authors must indicate their specific contributions to the published work. This information will be published as a footnote to the paper. See the format in the attachment file-revision policies.

➔ **Response:** Thank you for your comment. We added the author contribution following the format in the attachment file-revision policies. The change was made and marked in red at page 1 in the Title page section, as '*Yen TS and Liu CA conceptualized the study and contributed to data analysis and interpretation and manuscript preparation and revision; Liu CA provided writing assistance and proofread the article; Chiu NC was involved in data interpretation; Chiu NC, Chiou YY, Chou YH, and Chang CY contributed to the discussion regarding the manuscript.*'

VIII. Please rearrange all the authors' affiliations with Department, University or

Institute, City, Postcode, Country, etc. Please see the format in the attachment (without any symbol or figure like * or ¹).

➔ **Response:** Thank you for your comment. We rearranged all the authors' affiliations with Department, University or Institute, City, Postcode, Country following the format. The changes were made and marked in red at page 1 in the Title page section as '*Tsung-Shuo Yen, Department of Radiology, Wei Gong Memorial Hospital, Miaoli County 351, Taiwan*

Chien-An Liu, Nai-Chi Chiu, Yi-You Chiou, Yi-Hong Chou, and Chen-Yen Chang, Department of Radiology, Taipei Veterans General Hospital, Taipei City 11217, Taiwan

Nai-Chi Chiu, Yi-You Chiou, Yi-Hong Chou, and Chen-Yen Chang, School of Medicine, National Yang-Ming University, Taipei City 11217, Taiwan'.

IX. Structured abstract: An informative, structured abstract of no less than 336 words should accompany each manuscript.

➔ **Response:** The Abstract was structured into the following sections, AIM, MATERIALS AND METHODS, RESULTS, CONCLUSION. The change was made and marked in red at page 4.

X. a) Key words: A list of 5–10 keywords should be given below the abstract, each separated by a semicolon (;).

➔ **Response:** A total of 5 keywords were given below the abstract and marked in red as '*Key words: phlebosclerotic colitis, ischemic bowel disease, calcification of the mesenteric veins, symptoms of phlebosclerotic colitis, computed tomography*'. Each of them was separated by a semicolon.

b) Core tip: Please write a summary of less than 100 words to outline the most innovative and important arguments and core contents in your paper to attract readers.

➔ **Response:** We wrote a summary of less than 100 words in the revised manuscript. The change was made below the Keywords section and marked in red at page 5 as ‘**Core tip:** *Phlebosclerotic colitis, which is almost exclusively observed in the Asian population, is a rare condition of ischemic colitis associated with the sclerosis and calcification of the mesenteric venous wall, resulting in the preferential involvement of the right hemicolon and complications during a relatively chronic clinical course. We reviewed the medical records and examined the correlation between the severity of venous calcifications and the clinical symptoms of phlebosclerotic colitis observed on computed tomography images. According to our findings, the extent of mesenteric venous calcifications strongly positively correlates with the number of episodes of active disease.*

c) **Audio Core Tip:** In order to attract readers to read your full-text article, we request that the first author make an audio file describing your final core tip. This audio file will be published online, along with your article.

➔ **Response:** We made an audio file describing final core tip according to these specifications. Please see the attachment uploaded in the Audio column.

XI. COMMENTS

Please provide the “Highlighted contents” here, which is a necessary content.

➔ **Response:** We added this part ‘COMMENTS’ in the revised manuscript. The change was made and marked in red at page 12-13.

XII. At least 30 references should be included, covering important publications cited in PubMed within the past 4 years. For seminal references, however, the publication date is not strictly limited.

➔ **Response:** Thank you for your kindly reminder and reviewers’ comments. We added several references for the revised manuscript. Phlebosclerotic colitis is a

rare disease, so that the references for this kind of disease were limited. A total of 29 references were used in the revision.

XIII. Tables 1 should be as **excel** format so that I can edit them easily.

➔ **Response:** Table was changed as excel format. Please see the attachment uploaded.

XIV. The graphs supplied should be decomposable (each part of your figure could be moved so as to easily edited). You can send it as excel, word or powerpoint format so that I can edit them easily. Thank you!

➔ ➔ **Response:** We provided figures at a resolution of 300 dpi as TIFF format. Each figure was in a separate file and the size was larger than 86 mm × 50mm.

#Reviewer 1 (Reviewed by 02670181)

The authors examined the relationship between the severity of venous calcifications and phlebosclerotic colitis symptoms, although the disease is so rare. I think that the results in this study is very informative and may open up the window to seek the pathophysiology of this disease.

1. Major Pints: The authors described that “The Spearman correlation analysis~~” in Line 15~17, Page 3 (in the Results part). I think that the authors should **show the dispersion diagram between the numbers of active disease episodes and the severity of mesenteric venous calcifications**, otherwise the readers cannot see the distribution pattern of the two factors.

➔ **Response:** Thank you for your comment. We added a dispersion diagram (Figure 6) and a description for demonstrating the relationship between the number of active disease episodes and the severity of mesenteric venous calcifications. The change was made in the Result section and marked in red at page 9 in line 3-4 as ‘*The dispersion diagram (Figure 7) displays the relationship between the number of active disease episodes and the severity of mesenteric venous calcification.*’

2. Minor point: In the legend of Figure 2, the authors described “the contrast enhanced CT study~~”. However, neither the aorta nor the IVC was enhanced. I think that CT scan was plain one. If the authors stick to the idea that the CT scan was performed after contrast enhancement agent injection, please show the evidence. If not, the CT scan had better be the plain one.

➔ **Response:** Thank you for your comment. We revised the description for the Figure 2. The change was made in the Figure legend, which is a separate sheet and uploaded in the Supplementary Material column, as ‘Figure 2. **KUB and non-contrast enhanced CT**. A 56-year-old male suffered from right upper quadrant abdominal pain and fever. A: The KUB showed threadlike calcifications (arrows) at right abdomen; B: The **non-contrast** enhanced CT study revealed calcifications (arrows) at tributaries of mesenteric vein and wall thickening of ascending colon. The diagnosis is phlebosclerotic colitis with active episode.’ The change was marked in red.

Reviewer 2 (Reviewed by 00068625)

1. The problem presented in the paper has been discussed for several years, but it still remains actual topic. The paper is organized in a clear and easy to understand manner. The report is well-illustrated with informative and impressive radiological images but the results are based on a weak statistical basis, especially as **the three asymptomatic patients were included in the analysis.**

➔ **Response:** Thank you for your comment. We added additional information on the 3 asymptomatic patients. Although the three patients had no obvious clinical symptoms, we found that their CT imaging showed edematous thickening of the colonic wall and fat stranding of the surrounding mesentery which indicated inflammatory process of phlebosclerotic colitis. We added additional descriptions in the revised manuscript and the graphs in Figure 6. The changes were made in the Result section and marked in red at page 8 in line 24-26 and at page 9 in line 1-2 as *‘Three patients exhibited no apparent symptoms; however, the CT imaging findings of these three asymptomatic patients were bowel wall thickening and fat stranding at the paracolic gutters of the involved colon (Figure 6), which were typical imaging characteristics of this rare disease.’* and in the Discussion section at page 10 in line 17-18 *‘In the present study, although 3 patients exhibited no apparent clinical episodes of active disease, their CT imaging findings were typical of this disease (Figure 6).’*

2. The results of the statistical analysis should be attached to the table.

➔ **Response:** Thank you for your comment. We added the median and interquartile of the score of the severity of venous calcifications into the Table 1. The change was made and marked in red in Table 1.

3. Literature citations are appropriate and adequate for Retrospective Study although some of them should be improved in accordance with the rules of the journal. In Table 1 abbreviations are not defined e.g. HCC, ESRD.

➔ **Response:** Thank you for your comment. We added the definition of abbreviations, including HCC and ESRD, which were defined as *‘HCC, hepatocellular carcinoma; ESRD, end stage renal disease.’* The change was made and marked in red in Table 1.

#Reviewer 3 (Reviewed by 02959461)

The authors report 12 cases of Phlebosclerotic Colitis, a very rare disease which – according to the authors - to be restricted to the Asian population. So far only few cases have been reported, mostly reports of single or up to three cases. Therefore the authors report a relatively large number of cases with this disease. It is important to help the clinically interested reader to keep this rare disease in mind. The report is well-illustrated with informative and impressive radiological images. A case of one patient is well illustrated with subsequent CT scans over several years.

1. Major points: The cases were identified by reviewing radiological records / CT-scans. Accordingly, not all patients with radiological findings showed symptoms. Considering the fact, that the diagnosis should be made by clinical and radiological features, it seems doubtful to me, whether all patients fulfilled the criteria of Phlebosclerotic Colitis (or rather had asymptomatic phlebosclerosis). This should be commented by the authors (limitations of the study). Also more detailed information on the correlation of symptoms and radiological findings would be informative (for example a dot plot “symptoms vs. radiological score”), as well as additional information on the 3 (out of 12!) patients without symptoms (did they show radiological signs of colitis?).

➔ **Response:** Thank you for your comment. We added additional information on the 3 asymptomatic patients. Although the three patients had no obvious clinical symptoms, we found that their CT imaging showed edematous thickening of the colonic wall and fat stranding of the surrounding mesentery which indicated inflammatory process of phlebosclerotic colitis. We added additional description in the revised manuscript and the picture in Figure 6. The changes were made in the Result section and marked in red at page 8 in line 24-26 and at page 9 in line 1-2 as *‘Three patients exhibited no apparent symptoms; however, the CT imaging findings of these three asymptomatic patients were bowel wall thickening and fat stranding at the paracolic gutters of the involved colon (Figure 6), which were typical imaging characteristics of this rare disease.’* and in the Discussion section at page 10 in line 17-18 *‘In the present study, although 3 patients exhibited no apparent clinical episodes of active disease, their CT imaging findings were typical of this disease (Figure 6).’*

2. Regarding statistics, it is not clear, why single-tailed testing was applied- for my understanding

this is not appropriate considering the hypothesis. The findings are based on weak statistical methods, especially considering, that three patients without symptoms (and therefore possibly without the proposed diagnosis) were included in the analysis.

➔ **Response:** We used single-tailed testing is for the directional hypothesis, however, thank you for your comment that it's not appropriate considering the hypothesis. We changed to use a double-tailed testing to examine the hypothesis. The change was made in Statistical analysis of Material and Methods section and marked in red at page 6 in line 25-26 as '*A P value less than 0.05 was considered to indicate a significant correlation between the data sets, and a **double-tailed** test was used.*' The result was not changed by using Spearman's correlation analysis in SPSS.

3. No information is given on the treatment / treatment options. Considering the poorly known disease, the opportunity should be taken to mention possible treatment strategies (ideally with regard to the patients under investigation: did the diagnosis / radiological findings have clinical relevance in terms of a specific treatment in the reported cases).

➔ **Response:** Thank you for your comment. We added the information on the possible treatment strategies (with regard to the patients under investigation). The change was made in the Discussion section and marked in red at page 11 in line 20-25 as '*Previously, the majority of phlebosclerotic colitis patients underwent surgery; however, at present, conservative treatment with close follow-up is preferred if there are no signs of bowel compromise^[26-28]. Surgery has been suggested for patients with severe complications, such as intestinal obstruction, perforation, peritonitis and sepsis. The patients in our study received only conservative treatment because they lacked any complications that would require surgical treatment.*'

4. Minor points: Most patients suffered from ESRD or malignant disease. It would be interesting to **discuss possible etiologic aspects of the disease regarding malignancy or ESRD.**

➔ **Response:** Thank you for your comment. We added more descriptions to discuss possible etiologic aspects of the disease regarding ESRD. The change was made in the Discussion section and marked in red at page 9 in line 20-27 and at page 10 in line 1 as '*Six patients with phlebosclerotic colitis in our studies suffered from end-stage renal disease (ESRD), all of whom ingested Chinese herbs for different periods. The incidence of ESRD in Taiwan is the highest in*

the world, and there is an evidence that Chinese herb nephropathy is a significant cause of ESRD in Taiwan^[18]. Chang et al.^[19] indicated that these absorbed substances enter the venous return, potentially damaging veins. Moreover, several studies^[19-21] reported that certain substances or toxins from ingested Chinese herbs may contribute to phlebosclerotic colitis. Therefore, we propose that ESRD correlates with phlebosclerotic colitis. The relationship between ESRD and phlebosclerotic colitis requires further investigation.'

5. The manuscript's presentation is adequate, the readability compromised by some language problems. Suggestions:

6-1 p. 1 Introduction, line 3: ... almost exclusively observed...

- ➔ **Response:** Thank you for your comment. We added the word 'exclusively' in the Introduction section. The change was made at page 6 in line 5-6 as '*Phlebosclerotic colitis, which is almost **exclusively** observed in the Asian population^[3-7],....*'

6-2 Discussion, line 5: ... is chronic...

- ➔ **Response:** Thank you for your comment. We replaced 'chronically' with 'chronic' in the Discussion section. The change was made at page 9 in line 14 as '*The clinical course of phlebosclerotic colitis is **chronic**,....*' The change was marked in red.

6-3 Table 1: abbreviations are not defined: HCC, ESRD. UC is explained but not mentioned in the table.

- ➔ **Response:** Thank you for your comment. UC was written by mistake, and we deleted it. Moreover, we added the definition of abbreviations, including HCC and ESRD. The changes were made in Table 1 as '*HCC, hepatocellular carcinoma; ESRD, end stage renal disease.*' The change was marked in red and the deletion of 'UC, Ulterative colitis' was made.

- 3 References and typesetting were corrected

- ➔ **Response:** We corrected all references using A CrossRef DOI®, which link is <http://www.crossref.org/SimpleTextQuery/>, and the format of the World Journal Gastroenterology.

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,

Chien-An Liu, MD

Department of Radiology,

Taipei Veterans General Hospital,

Taipei City 11217, Taiwan, R.O.C.

E-mail: caliu@vghtpe.gov.tw

Telephone: + 886-2-2871212