Author’s response to reviews

Title: Social-Economic Analysis of Patients with Sjogren's Syndrome Dry Eye in East China: a cross-sectional study

Authors:

Wang Yao (792676901@qq.com)
Qihua Le (qihuale_eent@163.com)

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Author’s response to reviews:

Professor Guangde Tu

Editors-in-Chief, BMC Ophthalmology

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Dear Prof. Tu:

On behalf of the co-authors, we are submitting the revised manuscript entitled "Social-Economic Analysis of Patients with Sjogren’s Syndrome Dry Eye in East China" for consideration as a publication in BMC Ophthalmology. We sincerely appreciate the positive and constructive comments and suggestions from the editor and reviewers on our manuscript. We make substantial revisions in our manuscript according to the comments. We hope that the revisions make the manuscript better and meet the requirement of publication in BMC Ophthalmology.

This work has been carefully checked to correct linguistic errors by a native speaker (Daniel Cordova, as we mentioned in the acknowledgement). Written permission is obtained from Mr. Cordova before the submission. We guarantee that this work has not been published elsewhere and is not under review with any other journals. All authors have approved the manuscript for submission. And all authors have no proprietary or commercial interest in any of the materials discussed in this article. If it is published in BMC Ophthalmology, it will not be reprinted elsewhere in any languages in the same form without the consent of publisher, who holds the copyright.
We thank you for considering this paper and look forward to receiving your decision and referee's reviews.

Yours sincerely

Qihua Le M.D., Ph.D.
Dept. of Ophthalmology
Eye& ENT Hospital of Fudan University,
No. 83, Fen Yang Rd,
Shanghai, 200031, China

Point-to-point Response Letter

Ying Li (Reviewer #1):

This article investigated the medical cost and parameters of dry eye in Sjogren's syndrome dry eye (SSDE) and non-Sjogren's syndrome dry eye (non-SSDE) patients, and concluded that medical expense had a significantly correlation with psychological status and clinical severity in SSDE patients. The authors provided a novel view of SSDE and reached a meaningful conclusion and the article is worth to be published. However, major revision is still needed to reach the publishing criteria.

1. The introduction part is quite redundant and off the theme. The authors should talk more about the difference between SSDE and non-SSDE, the economic burden and related psychological impact, rather than the causes of DE.

Author's reply: Thank you for your advice. We make substantial revisions in the introduction. (Page4-5, line 41-64)

2. The Methods part is confusing and obscure. There is no clear definition of study and control group. The authors should make clear of the sources of SSDE and non-SSDE patients and described two groups separately instead of mixing them up. And the authors don't have to list the OSDI questionnaire, which is widely used and accepted. Instead, they should talk more about their own designed questionnaire.
Author’s reply: The diagnostic criteria for Sjogren's syndrome used in the study are illustrated in the method part (Page 5-6, Lines 71-84). Moreover, we delete the details of OSDI scale and make the revisions in the paragraph about the details of our questionnaire (Page 7, line 107-109, line 117-119).

3. The authors should also avoid repeating too many numbers from tables to make the Results part more concise. Also the numbers in the tables should be presented more scientifically according to the distribution of data. And the statistic analysis method should be clarified in the table footnote.

Author’s reply: Thank you for your suggestion. We delete the repeated numbers and make the revisions in the Result part to make it more concise. Since only one patient in non-SSDE group uses Chinese medicine and auxiliary therapy simultaneously, the “average value” and “median value” are not applicable in this case. Therefore we record the expenditure of this single patient in the Range part. Moreover, the statistical analysis methods have been clarified in the table footnote during the revision.

4. The authors should also be more cautious about citing references. In page 13, line 233, the authors mentioned that "Many studies had been confirming…and DE", but they only cite one study and the only cited reference is Corrigendum. I really doubt whether the authors check the paper they cited.

Author’s reply: We add relative references in the revision (Page 12, line 222, reference 16-20).

5. Finally, it will be necessary for the authors to have the paper carefully edited by nativespeakers for proper English usage.

Author’s reply: The paper has been carefully edited by a native speaker, who is acknowledged at the end of paper and in the cover letter.

JooYoun Oh (Reviewer #3):

This study deals with an interesting subject and evaluates the economic effect of dry eye in Sjogren's syndrome patients.
1. The major limitation of the study is a small sample size for this type of socio-epidemiological study. The authors had better increase the number of participants if available or should emphasize this limitation in Discussion.

Author’s reply: Thank you for your suggestion. We address this limitation in the discussion. (Page15, line 272-273)

2. Was the "medical expenditure" in this study the one related to ocular disease or did it include all the medical expense patients spent for their general condition, not only on ocular disease? The explanation for "medical expenditure" should be provided in detail.

Author’s reply: Only the expense on the medical treatment for SS and DE were included in this study. Treatment costs aimed at the other diseases were excluded. We address this issue in the revision (Page7, line 107-109).

HamidrezaMoein (Reviewer #4):

Authors investigated the annual medication/indirect/auxiliary expenses among patients with sjogren's syndrome dry eye (SSDE) versus non-SSDE. They also compared the clinical signs of dry eye disease such as tear break up time (TBUT), corneal fluorescein staining, and schirmer's score between the groups. In addition authors calculated the ocular surface disease index (OSDI) and self-rating anxiety scale (SAS) in two groups and correlated the values with expenditures. Their results demonstrated the total expenditure, medication expenditure, and indirect costs are higher among the SSDE patients compared to non-SSDE. Moreover, SAS score had a positive correlation with total medical and Chinese expenditures in the SSDE group. On the other hand, OSDI had a positive correlation with total medical expenditure paid by individual patients (not covered by the insurance) in the non-SSDE. There are major points that need to be addressed:

1. Translated questionnaires should be psychometrically validated or in another word being validated for both linguistic and cultural translation. This needs more time and effort to make sure the translated questionnaire maintains its reliability and validity to detect what it has been designed for in the original language. Other than language translation other steps should be considered to achievepsychometrical validation such as back translation and pre-testing in a pilot study. (Please refer to the WHO website for more detailed information:(http://www.who.int/substance_abuse/research_tools/translation/en/). These considerations were not made in this study, which makes the results biased.

Author’s reply: Three questionnaires are used in this study. Subjective perception and psychological impacts are involved in OSDI and SAS. The Chinese version of these two questionnaires have been validated and used by many studies (Reference10, Reference 27).
However, the data collected in the questionnaire specially designed for this study are all objective, such as medical treatment, medical expenditures and income. They can hardly be affected by patients’ subjective perception. Nevertheless, we have double checked the guidelines on the WHO website. The guideline is established for the translation of an already-existing English instrument to other languages. However, our questionnaire is not an already-existing instrument. It is a customized designed questionnaire in Chinese. Psychometrical validation is not applicable for this questionnaire.

2. The significant difference between SSDE and non-SSDE characteristics (educational background, retired subjects, time from onset of disease, and especially income) at baseline could potentially biased the results. This should be addressed in the discussion. For example level of education could affect how patients respond to the questionnaires.

Author’s reply: This is a cross-sectional study rather than a prospective study. Therefore we are unable to acquire the baseline of demographic data before the treatment. Moreover, the medical costs are more affected by the severity of the disease, rather than the demographic data. Anyway, thank you for your suggestion. It merits our prospective study in the future. Moreover, the discussion on the relationship between demographic data and the expenditure and psychological status was added. (Page 14 line 253-259, line 267-268)

2. This study is informative in a way that shows the economic burden of dry eye disease in Chinese population but it is not clear why authors correlated the expenditure with OSDI and SAS. This needs to be addressed in the introduction and then in the discussion. What is the main conclusion of positive correlation between SAS or OSDI and expenditures? How it can affect general healthcare policies or physicians practice?

Author’s reply: OSDI is a widely accepted scale to quantify ocular disability in cases of dry eye. We hypothesize that the severity of DE has a close relationship with the medical expenditures. Moreover, DE patients are shown to be more anxious than normal subjects. Earlier study also showed that anxiety was associated with excessive medical costs, including direct and indirect parts. Therefore we investigate the correlation between medical expenditure with OSDI and SAS. This issue is addressed in the introduction part in the revision (Page 4-5, line 58-62). The main conclusion of positive correlation between expenditure and OSDI/SAS is that the medical expense cost by SSDE patients positively correlated with the severity of DE and the patients’ anxious status. As for mild to moderate dry eye patients, clinical signs and symptoms are still the important index from the doctor’s perspective. The revisions are made in the manuscript (Page 14, line 259-262). Its impact on general health care is also added in the discussion (Page 11-12, line 206-209).
Specific comments:

1. Introduction: In the first paragraph, please the most updated definition of dry eye disease according to the recently published article by the "dry eye workshop II" in the Ocular Surface. (Ocul Surf. 2017 Jul; 15(3):276-283.)

   Author’s reply: Thank you for your suggestion. We update the definition of dry eye disease according to the article recently published in the Ocular Surface. (Page4, line 41-44)

2. Introduction: Lines 68,69; Cost of dry eye treatment in Asia has been published before (Cost of dry eye treatment in an Asian clinic setting. PLoS One. 2012;7(6):e37711) so maybe you can refer to this or specify that the cost of SSDE was not studied before.

   Author’s reply: We specify this content in the revised manuscript. (Page4, lines 54-56, 58-60)

3. Methods: The selection of SSDE group is not clear. Please add specific criteria that have been used in this study for diagnosis of Sjogren's syndrome.

   Author’s reply: The diagnostic criteria for Sjogren's syndrome used in the study are illustrated in the method part (Page 5-6, line 71-84).

4. Methods: The original SAS questionnaire suggests that patients with score of >36 be evaluated for general anxiety disorder (score of 45 if multiplied by 1.25 (36x1.25=45)). It should be explained why the scores were multiplied by 1.25 or add a reference, which used that scaling. In addition add a reference for choosing score of > 50 as symptoms of anxiety.

   Author’s reply: The SAS score is calculated according to the original literature, which was established by the designer of SAS (Reference 21). According to the previous report (Reference 10), we use the criteria that score >50 is considered as the presence of anxiety (Page7, line 115-117).

5. Methods/Table 1: The questions regarding the treatment are general and not specific for the dry eye disease. Please clarify whether these questions were asking for specific treatments for dry eye disease or Sjogren's syndrome? Since it has not been specified in the questionnaire is this possible that patients included their other treatment medication (such as their medication for controlling blood pressure or blood glucose or etc.) expenditures in this calculation?
Author’s reply: Thank you for your advice. The questions on the medical treatment are only focusing on the treatment of SS and DE. Expenditures on the treatment for other diseases are not included in the calculation. We clarify it in the revision (Page 7, line 107-109).

6. Results: Lines 186-187, Please add the average number of OSDI scores and SAS scores with separate p values for both SSDE and non-SSDE groups.

Author’s reply: These data were listed in TABLE 5. Regarding the comments from the editor and the other reviewers, the data were not repeated in the text part of Result (Page 23, TABLE 5).

7. Results: line 188, Please describe in details what do you mean by "symptoms of anxiety"? Does it mean that those number of patients had SAS score of >50?

Author’s reply: Yes. "Symptoms of anxiety" mean that the patients had SAS score >50. Sorry for the unclear description. We make the revision in the sentence to make it clear. (Page 7, line 116-117)

8. Results: Line 188, please add P value for comparing number of patients with anxiety in the SSDE vs. non-SSDE.

Author’s reply: P value is added in the revision. (Page 10, lines 173)

9. Results: Please describe if patients Sjogren's syndrome also were using other oral systemic medication as part of their disease treatment? Does that included in the total amount of money calculated or not?

Author’s reply: Apart from oral systemic treatment of Chinese medicine and ocular topical treatment, some SSDE patients have had oral systemic western medications including hydroxychloroquine and/or corticosteroid. The expense is included in the calculation during the revision. We also make the revision in Figure 1 to make it clear.

10. Discussion: It is important to explain if all the study patients had insurance and if they had different or similar insurance coverage. This is crucial to be clear since it can affect the amount of money they spent out of pocket.

Author’s reply: This issue is addressed in the revision. (Page 9, line 156-157)
11. Discussion: Line 245, Please describe how SSDE or non-SSDE may have affected the shelter and food cost? This is vague.

Author’s reply: In order to save time, SSDE patients are more willing to visit different hospitals (eye hospital for the treatment of DE, general hospital for the treatment of SS, and Chinese medicine clinic) in one day. Some patients accommodate in the hotel near the first hospital on the night before clinical visit to avoid traffic and to finish the clinical appointment at the first hospital as early as possible. Transfer from one hospital to another one also forced the patient to dine out, which lead to a higher food costs. Therefore the SSDE patients are likely to spend more costs on transportation, food or even accommodation. The revisions are made in the discussion part. (Page13, line 231-233).

12. Discussion: Please add relative articles about the cost of treatment in other countries into the discussion and compare with your results. (e.g., Cost of dry eye treatment in an Asian clinic setting. PLoS One. 2012;7(6):e37711)

Author’s reply: The revision is made in the discussion. (Page11, lines 187-188)

13. Figure1 legend: Please be consistent on how to refer to figures. For example in the last line "c" is put in parenthesis but this has not been done with the other figures.

Author’s reply: Thank you for your advice. The mistake is corrected in the figure legend. (Page18, line 332)

14. Table 3: In some instances instead of a range one number is written in the table. Please correct accordingly.

Author’s reply: Only one patient in non-SSDE group uses Chinese medicine and auxiliary therapy simultaneously. The “average value” and “median value” are not applicable in this case. We record the expenditure of this single patient in the Range part.

15. Table 5: on line 2, please change ST to S1T.

Author’s reply: The revision is made in TABLE 5.
GökhanPekel (Reviewer #2):

The authors reported a manuscript entitled 'Social-Economic Analysis of Patients with Sjogren's Syndrome Dry Eye in East China: a cross-sectional study'. The manuscript is well written. Overall the conclusion part is not attractive or interesting. My specific comments are written below. 1. The hypothesis of the study is not clear. All of the medical conditions (diseases) have economic burden. What is the special situation for Sjögren Syndrome? 2. The sample size is very small for this kind of study. 3. The figures (graphics) may not be necessary. 4. The medical expense data may be explained in detail by giving the exact prices for the products.

Author’s reply: The hypothesis of this study is that the medical costs for SSDE had a relationship with its clinical severity and patients’ psychological status. We made the revisions in the manuscript. The limitation of sample size is also addressed in the discussion. We also make additional revisions in the figure to provide more details about the therapeutic regimens in both SSDE and non-SSDE group.