PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Disease burden from COVID-19 symptoms among inpatients at the temporary military hospitals in Wuhan: A retrospective multi-center cross-sectional study
AUTHORS	He, Mai-hong; Li, Xiaoxiao; Tan, Qing; Chen, Yong; Kong, Yue; You, Jian-ping; Lin, Xian; Lin, Ying; Zheng, Qing

VERSION 1 – REVIEW

REVIEWER	Vasileiou, Eleftheria The University of Edinburgh, Usher Institute
REVIEW RETURNED	30-Jan-2021

GENERAL COMMENTS	This is a well designed, conducted and written cross-sectional study which aimed to determine the burden of COVID-19 illness among inpatients based on symptom duration and other sociodemographic patient characteristics in three hospitals in China. Abstract: line 59 - please change 'line regression' to 'linear regression' Methods: Investigators excluded inpatients with pre-existing medical conditions. These could have affected findings in the following two ways: a) the severity and duration of patients in this study may have been milder and shorter respectively and b) the exclusion of patients with a pre-existing psychiatric disease could have explained the short duration of reported anxiety and depression experienced during hospitalisation. It would thus be helpful if authors could bring the aforementioned points a and b to readers attention and include these potential explanations in the discussion section. Discussion: Self-reported bias is highly likely in this study given that information on symptoms duration prior hospital admissions was self-reported. Information bias could be also present. By reading the paper it does not seem that a laboratory test was carried out during hospital admission to confirm that a patient's symptoms were indeed due to SARS-CoV-2 virus and not other respiratory infections. The likelihood of the above bias should also be added as potential limitations of the study.

REVIEWER	Kretchy, James-Paul Central University, Public Health/Medical Microbiology
REVIEW RETURNED	02-Feb-2021

GENERAL COMMENTS	Do not begin sentences with abbreviations. E.g. BOD in the beginning of discussion section must be written in full. Replace "coronavirus diseases 2019" with the standard name "COVID-19" in the title

REVIEWER	Kamolz, Lars Medical University of Graz, Department of Surgery
REVIEW RETURNED	03-Feb-2021

GENERAL COMMENTS	I think that the topic is of interest, but there are several factor, which have to be changed or discussed: In Germany and Austria, one of the main COVID symptoms was the loss of the sense of smell and taste. For many people it was down for a long period of time and that was perceived as very restrictive and a major burden for a lot of patients. Were these symptoms not present in Wuhan and why were they not recorded and evaluated? The limitations are not mentioned and discussed in profound way! Please do so! The discussion is superfifcial too! I think that a more prfound discussion of this topic is requested and needed!

REVIEWER	Elimian, Kelly Nigeria Centre for Disease Control
REVIEW RETURNED	09-Feb-2021

GENERAL COMMENTS	This is an interesting manuscript and its obvious that the authors have made a concerted effort to get ht manuscript to this state. However, I had a challenge in understanding the 'focus' of the study. The use of DW, which is a method of describing BOD, and DALYs seem confusing--a focus on one of them would have been more concise for me and perhaps many readers. Overall, I feel the authors put too many information in one paper, without adequate synthesis of the findings both in the abstract and the main text. Errors and unclarity in some sentences also need to be revised. Measures of the duration of hospital stay and symptom (i.e. day) need to be specified in your tables.

VERSION 1 – AUTHOR RESPONSE

Reply to Reviewer 1:

We would first like to thank you for affirming the design, conduct, and presentation of our manuscript. We are very appreciative of your comments on the deficiencies in our manuscript.

To point 1 about Abstract:

The term 'line regression' has been revised to 'linear regression.' (line 67 in tracked version)

To point 2 about Methods:

We would like to thank you for your constructive advice on these aspects. Accordingly, we have discussed these issues at the end of the end of discussion section. (line 515-518 in tracked version)

To point 3 about Discussion:

We recognize that there is likely some bias in the inpatients' self-reports. Because this was a retrospective study based on the existing medical records that were generated during the emergency non-war military operation medical service, rather than a prospective study based on a prior design and intervention for the purpose of the study, the information in the medical records is not ideally suited for every aspect. However, the treatment of COVID-19 in Wuhan was an emergency and, realistically, the duration of symptomatology before admission relies on the self-report of the patients. The inpatients' self-report is, thus, the most reliable source of information in this case. Thus, an adjustment should be made for the self-report bias. Considering the relatively large sample, the macroscopic trend could be detected by statistical analysis, despite the potential bias. We discuss self-reported bias as a potential limitation of the study in strengths and limitations portion (in discussion section) of the manuscript.

We agree that the discussion about the laboratory test in our manuscript is not clear enough, and this could confuse the reader. In the third paragraph of the *Method/Selection of the population groups* section*,* we have added an explanation about the diagnostic methods for COVID-19. In the *Diagnosis and treatment standard of COVID-19 (7th edition)* published by the PRC central government, the laboratory tests for COVID-19 are clearly specified (line 179 in tracked version). Therefore, we thought it unnecessary to make a detailed statement in the manuscript in this regard. We have added a comment in the paragraph to indicate the criteria for laboratory tests.

Reply to Reviewer 2:

Thank you very much for your important comment about our manuscript. We are very sorry for the incorrect name in the title and discussion.

To point 1:

We agree with your comment; the expansion for the abbreviation "BOD" has been provided at the beginning of the discussion section. (line 421 in tracked version)

To point 2:

Thank you for this comment. The word "coronavirus diseases 2019" in the title was replaced with "COVID-19". (line 1 in tracked version)

Reply to Reviewer: 3

We greatly appreciate your valuable comments that point out some weaknesses of our study.

To point 1 about "loss of the sense of smell and taste":

It is true that loss of the sense of smell and taste is among the COVID-19 symptoms reported worldwide. We had also considered these symptoms in the study process. However, we excluded these symptoms due to the following reasons:

First, as a retrospective study, the data available and the practice that was followed were subject to existing medical records already generated by the three temporary military hospitals. Wuhan, China, experienced a large-scale epidemic of the disease at a time when there was limited knowledge about COVID-19. Despite this and many other disadvantages, China's health authorities attempted to ensure proper diagnosis and provide appropriate treatment protocols/standards for COVID-19 management in the early stage of the pandemic. However, the earlier versions of the protocols/standards had some shortcomings, mainly due to lack of knowledge about the disease. In our study, all the medical records were based on the 7th edition of the protocol/standard, in which the symptom of loss of the sense of smell and taste was not included in its clinical characteristics section. Considering the urgency of diagnosis and treatment, and the heavy workload for emergency rescue practitioners, during staff rounds of COVID-19 patients, during consultations, and during medical record entry, only the symptoms listed in the protocol/standard were looked into. Thus, very few records of loss of the sense of smell and taste are present in the medical records data. Consequently, we could not use this data in the study. Furthermore, a Korean study also did not consider the loss of smell or taste as an independent symptom in the early stages of the COVID-19 pandemic (reference 16). Perhaps, this too was because of a similar reason.

Moreover, inpatients usually present with the acute stage of the disease, during which loss of smell could possibly also be due to some other underlying respiratory symptoms, such as stuffy nose (which, in the Chinese language, is similar to mild dyspnea) or sore throat. The loss of taste could be due to some digestive system conditions, such as anorexia. Thereby, the loss of smell and taste could possibly have been placed under the respiratory and gastrointestinal symptoms to a large extent. When we calculated the disease burden of respiratory and gastrointestinal symptoms in our study, it could have amounted to that caused by the loss of smell and taste is included in the total.

Meanwhile, to the best of our knowledge, in most cases loss of smell or taste is usually more noticeable after the patient leaves the hospital, when other acute symptoms gradually disappear. Thus, we believe that loss of smell and taste should be treated as sequelae of COVID-19 rather than as the main symptoms in inpatients with the acute stage of the disease. Considering our study mainly focuses on the disease burden caused by the symptoms of the inpatient, loss of the sense of smell and taste should not be considered in this study.

We also discussed this issue in limitation part (line 493-502 in tracked version).

To point 2 about limitations and discussion:

We agree with you that the discussion for the COVID-19 study should be more profound, so that it could help in controlling the spread of the disease. We have tried our best to improve it. New points are added at the beginning of the Discussion section (line 401-420 in tracked version). Further, we have also revised the limitations section given at the beginning of the manuscript. (line 88-99 in tracked version) We also supplemented this with some more limitations being added to the end of the discussion section to address the shortcoming of this study. (line 488-519 in tracked version)

However, the original intention of our study is to give the government and healthcare management teams some macroscopic decision-making information from a public health perspective. We believe that the existing discussion is sufficient for this aim; also, based on current study data and statistical results, it is difficult to draw more definite discussion points. This section would become quite overwhelming if we were to discuss both overarching issues at the public health management level as well as the detailed microscopic issues at a clinical or molecular biological level. Besides, we also had to make note of the word counts given in the *BMJ Open* guidelines (4000 words). Although this is flexible, exceeding this would markedly impact the readability, as the journal points out.

Reply to Reviewer 4:

We would like to thank you for writing that "This is an interesting manuscript, and it's obvious that the authors have made a concerted effort…" We also appreciated the constructive criticism and suggestion. We have addressed all the points raised, as summarized below.

To point 1:

1. The overall structure of the manuscript:

Our study design is a simple step-by-step process that is not difficult to be understood by readers.

1) Establishing specific disease weights (DWs) by COVID-19 main symptoms;

2) Using the DWs to carry out a burden-of-disease (BOD, which quantitatively reflected by DALYs) empirical study on patients in three temporary military hospitals in Wuhan

3) Analyzing if some factors (age, gender, symptom duration before hospitalization, length of stay, body mass index, and native place) impact the BOD;

4) Based on the statistical results, give public health management suggestions.

BMJ Open does not require number headings, and it may cause some confusion in regard of subheadings. For this reason, we reedited the headings per guidelines: first level (Bold, All caps; line 100, 161, 280, 400, and 520 in tracked version) and second level subtitles (Bold, Sentence case).

2. The method section:

In the method section, we provided information on the following: 1) the selection of the population groups, 2) method for establishment of DWs, 3) data extraction process from the medical records, 4) the DALY algorithm, and 4) method of statistical analysis. This may have made this section slightly long; however, we believe that these are all necessary details for readers to understand the study in a more comprehensive manner.

3. The result and discussion section:

In the result section, baseline information of the selected medical record should be first given to the reader. Therefore, patient characteristics and duration of each symptom by demographic and severity were given before the result of DWs. Then, DWs results were given, which formed the basis for calculation of DALYs. Finally, we provide parametric statistics results of DALYs.

In the discussion, we focus on the disease burden and corresponding public health management, mainly based on results of DALYs' statistics.

4. The logic of the study:

Our study focuses on the quantification of the inpatient disease burden caused by COVID-19 based on the methodology proposed by the WHO. According to the methodology, the BOD is estimated by disability-adjusted life years, which is calculated by adding together years of life lost (death case) and the healthy years minus those lived with symptoms and disability. If we do not

consider death, the BOD can be simplified and be considered as the latter calculation alone. When we subtract healthy years by those lived with COVID-19 symptoms, we should use disease weights (DWs) for the symptoms. Thus, BOD, DALYs, and DWs are integrated into one methodology system, which should not be divided into separated studies. This is because BOD could not be quantitatively reflected without calculating DALYs, while DALYs also could not be calculated without symptoms' DWs. Thus, our logic was to first establish a set of DWs of the main symptoms of COVID-19, based on which DALYs could be calculated and BOD could be quantitatively reflected. If only DWs of COVID-19 were assessed, an empirical study would be needed to prove the feasibility. Only DALYs was also not discussed since there is no proper DWs for each main COVID-19 symptom in the WHO's DWs list. Besides, if we split the study into two or more parts, then readers cannot get the full picture of the COVID-19 inpatient's disease burden caused by symptoms, thus precluding an understanding of the research process. Also, the process used herein could be adapted and used as a reference for their public health study or practice.

Furthermore, we believe that the study methodology that integrated both establishing specific DWs for disease symptoms and calculating empirical DALYs is a feasible way for disease burden research for a rare disease that is not included in WHO's Global Burden of Disease program. For example, in our reference 15, Pei T et al. employed this strategy to calculate the disease burden resulting from chronic mountain sickness among young Chinese male immigrants in Tibet.

5. The abstract:

As regards the concerns pointed out in the abstract, please note that it has now been revised following the *BMJ Open* guidelines. (line 55-78 in tracked version)

To point 2:

We regret there were some errors and in some sentences and that some phrases were unclear. The manuscript has been carefully revised by a professional language editing service company Editage (www.editage.cn), to improve the readability. We hope that the revised manuscript now meets your expectations.

To point 3:

Thank you for pointing out our omission of the units in the tables. We have added in the measures of the duration of hospital stay and symptoms (i.e., day) in the tables.

We have put our best efforts into revising and improving the manuscript. These changes will not influence the content and framework of the paper. We have listed the changes within this document and have tracked them in the revised paper. We appreciate your considerate remarks and hope that the corrections will meet with approval.

Once again, thank you very much for your comments and suggestions.

VERSION 2 – REVIEW

REVIEWER	Vasileiou, Eleftheria The University of Edinburgh, Usher Institute
REVIEW RETURNED	14-Mar-2021

GENERAL COMMENTS	I would like to thank Authors for addressing all my suggestions. The manuscript now reads more clearly and additional important information has been added.

REVIEWER	Kamolz, Lars Medical University of Graz, Department of Surgery
REVIEW RETURNED	22-Mar-2021

GENERAL COMMENTS	I think that the paper is of interest and worth to be published; It hink that there is a need for language editing. Please do so!

VERSION 2 – AUTHOR RESPONSE

Reply to Reviewer 1:
We greatly appreciate your work on our manuscript. We would like to thank you for the following encouraging comment: “the manuscript now reads more clearly and additional important information has been added”.

Reply to Reviewer 3:
Thank you very much for your work on our manuscript. We greatly appreciate the fact that you consider that “the paper is of interest and worth to be published”.
Concerning language issues, we have sent the manuscript to a professional language editing service company, Editage (www.editage.cn), for the third time. It has been carefully revised to improve the readability. We hope that the revised manuscript now meets your expectations.

We have put our best efforts into revising and improving the manuscript. These changes will not influence the content and framework of the paper. We have listed the changes within this document and have tracked them in the revised paper. We appreciate your considerate remarks and hope that the corrections will meet with approval.

Once again, thank you very much for your comments and suggestions.