

### Spectrum of thyroid dysfunctions among hospitalized patients with non-critically ill coronavirus disease 2019: A cross-sectional study

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Reviewer – 1 information			
Date review assigned	30-Apr-23	Date review returned	01-May-23
Reviewer name	A	Affiliation	-
Email	-	ORCID	-
Do you have any conflict of interest with the author/s?	No	Do you wish to be disclosed to the author?	No

Reviewer's comments (09-May-23) [Please select "Yes" or "No"]		Author's response (14-May-23) [Please write a response if the reviewer's comment is "No". You must change the manuscript as per your response. Mention line numbers.]
1. Is the title appropriate?	Yes	
2. Is the research question or study objective clearly defined in measurable terms?	Yes	
3. Is the abstract accurate, balanced and complete?	No	We changed accordingly. P-2, lines: 33-34, 50, 51, 55.
4. Is the study design appropriate to answer the research question or achieve objective?	Yes	-
5. Are the Methods described sufficiently to allow others to repeat it?	Yes	-
6. Are the operational definitions and ascertainment of key variables given adequately?	Yes	-
7. Are the outcomes clearly defined?	Yes	-
8. Are statistics used appropriately and described fully?	Yes	-
9. Do the Results address the research question or objective clearly?	Yes	-
10. Are the tables and figures clear and appropriate to address the objective or research question?	Yes	-
11. Does the Discussion cover the main points of the paper?	No	We changed accordingly. P-8, lines: 171-173;
12. Are the strengths and limitations addressed?	Yes	-
13. Are the conclusions justified by the results?	No	We changed as per the instructions. P-10, lines: 230-232
14. Are the references up-to-date, and appropriate?	Yes	-
15. Is the standard of written English acceptable for publication?	No	We have corrected them as per the suggestions throughout the manuscript and highlighted them.
16. <b>Descriptive comments</b> to the authors (Divide it into MAJOR and MINOR points).		Respond and reflect it in your manuscript. If you refute, justify your argument using references. Mention line numbers.
<b>MAJOR points</b>		
1. Abstract should be more precise.		1. Has been revised providing a clearer summary of the key points.
2. Discussion should be more generous and logical. A few suggestions are given in the text.		2. We have expanded and improved the logic of the content based on the suggestions provided.
3. Conclusion needs to be corrected.		3. Carefully corrected.
4. Improvement of English is necessary.		4. Tried to improve the overall English language.
17. <b>Reviewer's Recommendation</b>	Major revision	

<b>Executive Editor's comments (09-May-23)</b>		<b>Author's response (14-May-23)</b> Please respond to all comments from the editor and reviewer(s). Indicate the line number(s) of the manuscript where the changes are done.
1.	Lines 51, 162, 168: delete p=ns for all	We have deleted and highlighted them. Lines 50, 151, 154, 160.
2.	Lines 66 and 68: Avoid repetition of "with COVID-19."	We have deleted and highlighted them. Lines 60, 62.
3.	Line 114: A 5% margin of error is customarily used. Please justify (with a reference) why you have used 10% error rate.	This is also acceptable. Ref.: <a href="https://apps.who.int/iris/handle/10665/40062">https://apps.who.int/iris/handle/10665/40062</a> . Sample size determination in health studies: a practical manual/ SK Lwanga and S Lemeshow. Page-2, example-2. Examples can be also found in the Oxford Handbook of Medical Statistics, 2 <sup>nd</sup> edition.
4.	Line 141: drop "one way ANOVA", just keep Kruskal-Wallis test	We have deleted and highlighted them. Lines 134, 346.
5.	Lines 269: There are so many references without having a full list of authors. BSMMU J uses the full list of authors. Drop et al.	We have provided the full author lists. Ref no: 1, 3, 8, 10, 13, 15, 16, 21, 23
6.	<b>Editor's Decision</b>	<b>Major Revision</b>

## Second round

<b>Executive Editor's comments (14-May-23)</b>		<b>Author's response (21-May-23)</b> Please respond to all comments from the editor and reviewer(s). Indicate the line number(s) of the manuscript where the changes are done.
<p>Thank you for sending a revised manuscript. Inadvertently the Editor's comments were not fully recorded in the comment sheet. Therefore, given further comments on the tables for your kind considerations. We shall appreciate receiving a revised manuscript.</p>		
1.	The issue of sample size is still there. You have answered in the author response sheet but I do not see justifications for choosing 10% error. The reference cited has calculations for various examples, 5% and 10%. You can do it for 20% even! But you have to justify (in the manuscript) why such a big error rate has been used.	1. Justified as advised. The revised sentence is "we took 10% margin of error as we thought it as the maximum acceptable error to give a satisfactory result"
2.	Are you generating hypothesis to be tested by another study? Then your analysis should not have so many subgroups. Now you have 10 subjects in so many cells.	2. Generating hypothesis is not the primary goal, therefore removed the subgroup analysis.
3.	The fall non-significant results are very likely for so many P values. Therefore, conclusions drawn by this study is not valid for so many instances. The root of this problem is a badly planned sample size. As per the objective, you do not need so many sub-groups either. I would suggest presenting results of TSH, T3, T4, CRP, D Dimer, ferritin, NLR and PLR for three group of COVID-19 patients (mild moderate severe) adjusted for age, sex and BMI in one table (Table 2) only. Age sex and BMI distribution in these three groups could be given in another table (Table 1).	3. Removed the subgroup analysis and reduced the table.

Reviewer – 2 information			
Date review assigned	3-May-23	Date review returned	19-May-23
Reviewer name	Dr. S M Rashed Ul Islam	Affiliation	BSMMU
Email	<a href="mailto:smrashed1620@yahoo.com">smrashed1620@yahoo.com</a>	ORCID	0000-0002-8164-5905
Do you have any conflict of interest with the author/s?	No	Do you wish to be disclosed to the author?	Yes

Reviewer comments (26-May-23) [Please select “Yes” or “No”]		Author’s response (31-May-23) [Please write a response if the reviewer’s comment is “No”. You must change the manuscript as per your response. Mention line numbers.]
1. Is the title appropriate?	Yes	
2. Is the research question or study objective clearly defined in measurable terms?	Yes	
3. Is the abstract accurate, balanced and complete?	Yes	Click or tap here to enter text.
4. Is the study design appropriate to answer the research question or achieve objective?	Yes	-
5. Are the Methods described sufficiently to allow others to repeat it?	No	Have revisited the Methods section to ensure that the description is comprehensive enough to enable others to replicate the study.
6. Are the operational definitions and ascertainment of key variables given adequately?	No	The operational definitions and ascertainment of key variables have been expanded upon to provide a more thorough and explicit explanation.
7. Are the outcomes clearly defined?	No	The outcomes have been carefully reviewed and further clarified to ensure that they are explicitly defined.
8. Are statistics used appropriately and described fully?	Yes	-
9. Do the Results address the research question or objective clearly?	No	Revised tables and text of the results. Removed subgroup analysis.
10. Are the tables and figures clear and appropriate to address the objective or research question?	Yes	-
11. Does the Discussion cover the main points of the paper?	No	We changed accordingly. P-8, lines: 171-173;
12. Are the strengths and limitations addressed?	No	Addressed in the last part of the discussion.
13. Are the conclusions justified by the results	No	We changed as per the instructions. P-10, lines: 230-232
14. Are the references up-to-date, and appropriate?	Yes	-
15. Is the standard of written English acceptable for publication?	No	We have corrected them as per the suggestions throughout the manuscript and highlighted them.
18. <b>Descriptive comments</b> to the authors (Divide it into MAJOR and MINOR points).		Respond and reflect it in your manuscript. If you refute, justify your argument using references. Mention line numbers.
<b>MAJOR points</b>  <b>Abstract</b> 1. Line 37: Was there any severe illness, as all the cases were non-critical COVID-19? 2. Line 41: Is there any severe form of COVID-19 under the non-critical COVID-19 category? 3. Line 49: Non-critical case category should be defined first; then, this result can be understandable. 4. Line 54: It can not be said that TFT has no significant association with the severity of illness,		1. Line-37: In the WHO’s guidelines. Noncritical cases include mild, moderate, and severe forms. 2. Line-41: Yes, sir. Please see WHO’s guidelines. Ref-2. 3. Line-49: This is a clinical paper, it is a very common term for clinicians. So, we just gave the WHO’s reference from where the reader can get the definition. There is little scope to define the categories in the abstract section.

<p>as the author has selected only the non-critical COVID-19 from a cross-sectional point of view.</p> <p>5. Highlights: Non-critical ill should be defined.</p> <p>6. Introduction: Line 49- Elaborate on the term spectrum; Line 75- add a reference after the line.....illness; Line 89 to 91- Can be accommodated to discussion if required.</p> <p>7. Line 104: Change the sentence: proven COVID-19 patient to COVID-19 infected patients.</p> <p>8. It is mentioned that the TFT function in critical /severe COVID-19 cases is already mentioned. Can you cite some articles both from regional and abroad sources?</p> <p>9. Why is it important to see the TFT values in non-critical cases?</p> <p>10. It is very difficult to comment on the deterioration of TFT function in patients without any history of Thyroid dysfunction. A study with follow-up of these cases or observation in pre-existing Thyroid patients could give a better view.</p> <p>11. Method: Please elaborate on the case selection criteria, Operational definition of COVID-19 categories. Maintain a chronology of points while writing the methodology section.</p> <p>12. Line 136: Mention the reference values.</p> <p>13. Line 139: Mention why these data were missing. Is missing data have any effect on the analysis of the result? How much percentage of data was missing? Can the result analysis be made only on the available data?</p> <p><b>Result:</b></p> <p>14. Please add a table on the patient's characteristics relating to COVID-19 status, symptoms, Status of hospitalized, vital signs, Need for oxygen inhalation, the reason for their hospitalization etc. It would be ideal if this article had two groups, one healthy group and another COVID-19 group, if possible. However, the analysis can be based on the COVID-19 clinical status, comparing all the parameters among the mild, moderate and severe groups. Here, many analysis showed that the parameter was found non-significant, making it difficult to draw a conclusion for the readers. Table 1 to 3 can be merged, highlighting the most important findings. Figure 1 can be omitted as it was already in table 1.</p>	<p>4. Line-54: Sir, it is only for noncritical patients. Line- 55.</p> <p>5. Highlights: Symptomatic COVID-19 patients without related complications- such as respiratory failure, ARDS, sepsis and septic shock, thromboembolism, and/or multiorgan failure including acute kidney injury and cardiac failure.</p> <p>6. Introduction: Line-49: Spectrum means all the possible; thyroid function abnormalities; Line-75: We added the reference (no-2) (L-70); Lines: 89-91: Euthyroid sick syndrome is one of the common thyroid function abnormalities in acutely ill patients.</p> <p>7. Line- 104: We changed it as per the advice (Line 99).</p> <p>8. Given references 7-9, 11-14.</p> <p>9. Importance: Most of the COVID-19 cases are non-critical. COVID-19 affects the TFTs mostly in critical patients. But non-critical patients can also have thyroid dysfunction. So, it needs to be evaluated.</p> <p>10. It is beyond our scope as we did not include patients with previous known thyroid dysfunction. There is little importance to see altered thyroid dysfunctions among already diagnosed cases.</p> <p>11. Method: Please see the 1 st paragraph of the Methods section. One can find the definitions of the severity of illness from the WHO's guidelines.</p> <p>12. Line-136: Added in the footnote of Figure-1.</p> <p>13. Line-139: These are taken from patients' medical records. Available data are mentioned in tables. We have analyzed among available data.</p> <p>14. We have rearranged our tables and figures differently with explanations as per the editor's suggestions. Figure-1 includes the spectrum whereas the Table-1 compares euthyroid vs. abnormal thyroid status- not the same.</p>
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<p><b>Discussion:</b></p> <p>15. The whole part of the discussion should be revised and rewritten on the basis of changes in the methodology, analysis plan, and study findings. Most of the statements were on COVID-19 cases, but this study was only a particular group of COVID-19 made it difficult to create a fair impression.</p> <p>16. Line 187-194, If these findings were necessary to mention, it needs to elaborate on the status of these 87 patients for better comparison. It is to avoid duplication of result descriptions in the discussion.</p> <p>17. Line 201: Move all limitations at the end.</p> <p>18. Line 209: ESS is addressed in this study, If not, the sentence may be removed. Same for autoimmune thyroiditis etc.</p> <p>19. Line 228 to 233: Can be omitted.</p> <p>20. In conclusion: Mention why the observation of thyroid status is important if the patients do not have any pre-existing thyroid diseases and if any thyroid dysfunction is found during COVID-19-infected hospitalized patients, what further follow-up and direction should be followed.</p> <p>21. Acknowledgment: Please mention the Physician, Doctor and other HCW for their kind help as they took the risk of their life while treating this case during the full-blown COVID-19 pandemic; all the patients and staff of the COVID-19 unit hospital for maintaining the IPC.</p> <p><b>Overall</b></p> <p>22. This analysis plan should be revised, and study findings may be shown according to the different clinical statuses of COVID-19 cases. Only the most important findings may be shared.</p> <p>23. This article may be transformed into Brief communication of correspondence type article if the journal committee allows it.</p> <p>24. English editing and grammar are required to be checked.</p> <p>25. Title: The title may be changed to Observation of thyroid functions among the COVID-19 infected Hospitalized patients in a tertiary care setting.</p>	<p>15. We have written the discussion according to the results.</p> <p>16. Line: 187-194: We have compared our findings (non-critical COVID-19 cases) with usual thyroid abnormalities as we have no control group.</p> <p>17. Line: 201- We moved them (L: 232-233).</p> <p>18. Line- 209: This is addressed in the discussion to find out the cause of different thyroid abnormalities in COVID-19.</p> <p>19. Line: 228-33: This is the paragraph where the limitations are written (L: 232- 233).</p> <p>20. In Conclusion: It is written as a rationale in the introduction section. Any viral illness may alter TFTs. Follow-up is needed for any thyroid abnormalities to see the recovery/ persistence.</p> <p>21. Acknowledgment: We have acknowledged.</p> <p>22. The most important finding of this study was to see the thyroid function abnormalities that have been displayed in our result section.</p> <p>23. We think, it will be difficult to accommodate several findings within a brief communication.</p> <p>24. We tried to improve by using software.</p> <p>25. Title: We want to keep our title as before. Because it describes the main findings of our study.</p>
<p>19. <b>Reviewer's Recommendation</b></p>	<p>Major revision</p>