

# Peer Review Overview



## Manuscript Title COVID-19 infection and thyroid function

Received	April 02 2022
1st Decision	May 20 2022
1st Revision Submitted	Jun 03 2022
2nd Decision	Jul 23 2022
2nd Revision Submitted	Jul 23 2022
Accepted	Jul 30 2022

## 1st Decision letter

**Reference:** ENDMTS-D-22-00011

**Title:** COVID-19 infection and thyroid function

**Journal:** Endocrine and Metabolic Science

Dear Dr. Alzahrani,

Thank you for submitting your manuscript to Endocrine and Metabolic Science.

We have completed the evaluation of your manuscript. The reviewers recommend reconsideration of your manuscript following revision. I invite you to resubmit your manuscript after addressing the comments below. Please resubmit your revised manuscript by Jun 10, 2022.

When revising your manuscript, please consider all issues mentioned in the reviewers' comments carefully: please outline in a cover letter every change made in response to their comments and provide suitable rebuttals for any comments not addressed. Please note that your revised submission may need to be re-reviewed.

Endocrine and Metabolic Science values your contribution and I look forward to receiving your revised manuscript.

Sincerely,

Fady Hannah-Shmouni, MD FRCPC

Editor-in-Chief  
Endocrine and Metabolic Science

## Comments from Editors and Reviewers:

### Reviewer #1:

Reviewer #1: Thanks for allowing me to review this paper titled 'COVID-19 infection and thyroid function'. Authors present a case series of 50 patients admitted to their institute with serial thyroid measurements. While this data may be of interest to a wide audience, there are several improvements that should be considered for this manuscript.

1. Was information on biotin supplementation sought and were those on biotin supplementation excluded?
2. Spellcheck and grammar:
  - a. Page 4: 220 million, correct spelling of Wuhan, China
  - b. Page 4: add bracket before KFSHRC)
  - c. Page 6: please correct the spelling of azithromycin page 6, tocilizumab page 6,
3. It would be very helpful to have a flowchart of patient selection and categorization of TFTs performed per severity category. For e.g., severity A had 13 patients and 13 baseline and 5 follow-up TFTs were performed etc.
4. Introduction: please cite PMID: 33180932 as one of the studies in the introduction
5. Methods: It is unclear how many patients for each category had follow-up TFTs. It seems that this was a prospective study in which case a uniform protocol of TFTs should have been followed but it seems that there is no clear pattern to collection of TFTs. If this was a retrospective study, that should be clearly stated and the rationale of different timing and frequency of TFT collection be provided.
6. Methods: please provide appropriate citation for CDC and WHO COVID-19 severity guidelines.
7. Results: For the section 'thyroid function assessment' I would suggest tabulating the findings of the 5 patients who had transient TFT abnormalities. This should include their sex/age, any relevant lab markers (CRP, ferritin, WBC, IL-6 etc.) and TFTs. I would avoid terming transient elevations of TSH as subclinical hypothyroidism unless the TSH was persistently elevated in a stable clinical setting.
8. In patients who had abnormalities of TFTs, were anti-TPO or anti-thyroglobulin antibodies checked?
9. Authors should also provide more details about each category of patients. For e.g., modifying table 1 with baseline characteristics (age, sex, etc.) stratified by severity would help. Please also provide information of length of hospital stay per severity class.
10. It also seems strange that 26% patients fell were under category A (completely asymptomatic) and 48% fell under category B that lacked evidence of any respiratory compromise in total constituting 74% of admitted patients. Why were these patients admitted in the first place? The inclusion of such a large number of asymptomatic or mild cases skews the conclusions about thyroid function in hospitalized

COVID-19 patients. Therefore, no conclusion can be drawn about differences in TFTs between mild and severe/moderate disease given the small sample of severe/moderate disease (n=13).

11. Please also discuss the proposed physiology of thyroid function changes in COVID-19 covered here  
PMID: 33559848

12. Authors should explicitly state the weaknesses of this study which are currently not listed. I would include the heterogeneity in frequency/timing of TFT collection, small number of severe disease, lack of ultrasound data, lack of disease severity markers etc.

13. Please share the prospective study protocol as a supplementary file

## Author's 1st Response Letter

### Response to comments from Editors and Reviewers:

#### Reviewer #1:

Reviewer #1: Thanks for allowing me to review this paper titled 'COVID-19 infection and thyroid function'. Authors present a case series of 50 patients admitted to their institute with serial thyroid measurements. While this data may be of interest to a wide audience, there are several improvements that should be considered for this manuscript.

Thank you very much for the great constructive comments. This has helped us a great deal to improve our manuscript

1. Was information on biotin supplementation sought and were those on biotin supplementation excluded?

Answer: The information on biotin and any other drug that may potentially change TFT were sought. This is mentioned in the methods (Line 77)

2. Spellcheck and grammar:

a. Page 4: 220 million, correct spelling of Wuhan, China

b. Page 4: add bracket before KFSHRC)

c. Page 6: please correct the spelling of azithromycin page 6, tocilizumab page 6,

Answer: Apology for these spelling errors, we have corrected them all (Lines 53, 54 and 68).

2. It would be very helpful to have a flowchart of patient selection and categorization of TFTs performed per severity category. For e.g., severity A had 13 patients and 13 baseline and 5 follow-up TFTs were performed etc.

Answer: Thank you for this excellent suggestion. We have included a flowchart as advised (Figure 1)

3. Introduction: please cite PMID: 33180932 as one of the studies in the introduction

Answer: We have included this important reference in the introduction and also in the discussion (Lines 61-65, 179-186).

4. Methods: It is unclear how many patients for each category had follow-up TFTs. It seems that this was a prospective study in which case a uniform protocol of TFTs should have been followed but it seems that there is no clear pattern to collection of TFTs. If this was  
Response to authors

a retrospective study, that should be clearly stated and the rationale of different timing and frequency of TFT collection be provided.

Answer: We recognize this shortcoming. This is a prospective study done at the beginning of COVID-19 pandemic. Although a clear protocol was written to be followed up, we faced some logistic issues related to the anxiety of the nursing and phlebotomy staff at that time who were hesitant to enter the rooms of the patients and also refusal by some patients of blood drawing on certain days. We have included this in the weaknesses of the study (Lines 237-240).

5. Methods: please provide appropriate citation for CDC and WHO COVID-19 severity guidelines.

Answer: We have added references for the CDC and WHO guidelines (reference 8 and 9, lines 82-83)

6. Results: For the section 'thyroid function assessment' I would suggest tabulating the findings of the 5 patients who had transient TFT abnormalities. This should include their sex/age, any relevant lab markers (CRP, ferritin, WBC, IL-6 etc.) and TFTs. I would avoid terming transient elevations of TSH as subclinical hypothyroidism unless the TSH was persistently elevated in a stable clinical setting.

7. Answer: Thank you for this excellent suggestions. We have added a table summarizing the laboratory and other data and modified the section on thyroid function assessment to minimize repetition (Table 2 and lines 133-135)

8. In patients who had abnormalities of TFTs, were anti-TPO or anti-thyroglobulin antibodies checked?

Answer: Unfortunately, only one patient (Patient # 5) had anti TPO and Antithyroglobulin Abs tested (Lines 135-137)

9. Authors should also provide more details about each category of patients. For e.g., modifying table 1 with baseline characteristics (age, sex, etc.) stratified by severity would help. Please also provide information of length of hospital stay per severity class.

Answer: this is an excellent suggestion. We have modified table 1 accordingly. It shows now the different variables for the whole group and by severity category (Table 1).

10. It also seems strange that 26% patients fell were under category A (completely asymptomatic) and 48% fell under category B that lacked evidence of any respiratory compromise in total constituting 74% of admitted patients. Why were these patients admitted in the first place? The inclusion of such a large number of asymptomatic or mild cases skews the conclusions about thyroid function in hospitalized COVID-19 patients. Therefore, no conclusion can be drawn about differences in TFTs between mild and severe/moderate disease given the small sample of severe/moderate disease (n=13).

Answer: Wee totally agree with the reviewer that the data is skewed towards milder spectrum of COVID-19. However, in real life, the majority of patients with COVID-19 have mild illness and therefore, this study might be more representative of the actual facts. The reason for admission of patients with mild disease is that this study was done in the initial phase of COVID-19 pandemic (May 2020) and at that time, there was significant uncertainty and anxiety. Many patients who would not be admitted today to the hospital were admitted at that time to isolate them and curtail the spread of the disease, an approach that has significantly changed with time. We have discussed this shortcoming (Lines 240-245).

11. Please also discuss the proposed physiology of thyroid function changes in COVID-19 covered here PMID: 33559848

Answer: We have included this important reference in the discussion of the pathophysiology of thyroid dysfunction in COVID-19 infection (Lines 187-194)

12. Authors should explicitly state the weaknesses of this study which are currently not listed. I would include the heterogeneity in frequency/timing of TFT collection, small number of severe disease, lack of ultrasound data, lack of disease severity markers etc.

Answer: We totally agree with reviewer that this study has some weaknesses and we have explicitly and extensively discussed them in this revised manuscript (Lines 233-245).

13. Please share the prospective study protocol as a supplementary file

Answer: We have shared the study protocol as a supplementary file

## 2nd Decision letter

**Reference:** ENDMTS-D-22-00011

**Title:** COVID-19 infection and thyroid function

**Journal:** Endocrine and Metabolic Science

### Comments from Editors and Reviewers:

Dear Dr. Alzahrani,

Thank you for submitting your manuscript to Endocrine and Metabolic Science.

We have completed the evaluation of your manuscript. The reviewers recommend reconsideration of your manuscript following revision. I invite you to resubmit your manuscript after addressing the comments below. Please resubmit your revised manuscript by Aug 06, 2022.

When revising your manuscript, please consider all issues mentioned in the reviewers' comments carefully: please outline in a cover letter every change made in response to their comments and provide suitable rebuttals for any comments not addressed. Please note that your revised submission may need to be re-reviewed.

Endocrine and Metabolic Science values your contribution and I look forward to receiving your revised manuscript.

Sincerely,

Fady Hannah-Shmouni, MD FRCPC

Editor-in-Chief

Endocrine and Metabolic Science

## **Reviewer 1**

Reviewer #1: I have reviewed the revised version and authors' modifications that are largely acceptable. One issue that remains is the lack of ability of these data to draw conclusions about the association between severity of disease and thyroid function.

### Highlights

Bullet 5: This thyroid dysfunction is mild and transient and does not correlate with the severity of Infection

Abstract lines 41-43 and 46-47 state

Results lines 41-43: There was no association between TFTs and the severity 42 of COVID-19 infection or the rate of admission to intensive care unit (ICU). TFTs in those 43 admitted to the ICU were not different from TFTs in those treated in the general floor.

Conclusions Lines 46-47 state: thyroid dysfunction during acute COVID-19 infection is rare, mild and transient and does not correlate with the severity of the illness or outcome of the disease.

Lines 164-167 state this association as follows

"However, there was no association between TFT and severity of illness in patients with different severity of the illness and no differences in TFT between those who needed ICU admission due to severe disease and those who were treated in the general ward."

These lines are alluding to a conclusion on this matter based on their study which is problematic and not supported by their data.

I recommend that authors state instead that their study was not adequately powered to detect an association between severity of COVID and TFTs given the various limitations of the study (skewed data, only n=2 in severity D group, inadequate/heterogeneous follow-up data and others) as stated in text by authors. These sections should be revised to avoid referring to any of the above-mentioned conclusions.

## **Author's 2nd Response Letter**

### **Response to comments from Editors and Reviewers:**

Reviewer #1: I have reviewed the revised version and authors' modifications that are largely acceptable. One issue that remains is the lack of ability of these data to draw conclusions about the association between severity of disease and thyroid function.

Thank you for your insightful review

## Highlights

Bullet 5: This thyroid dysfunction is mild and transient and does not correlate with the severity of Infection

Answer: We agree that this point is not well supported by the data. We have deleted it

Abstract lines 41-43 and 46-47 state

Results lines 41-43: There was no association between TFTs and the severity 42 of COVID-19 infection or the rate of admission to intensive care unit (ICU). TFTs in those 43 admitted to the ICU were not different from TFTs in those treated in the general floor.

Answer: this statement is deleted (page 2, line 41-43)

Conclusions Lines 46-47 state: thyroid dysfunction during acute COVID-19 infection is rare, mild and transient and does not correlate with the severity of the illness or outcome of the disease.

Answer: We have adjusted the conclusion to reflect the fact that the study may not be powered enough to show an association between COVID-19 and TFTs. (page 2, lines 46-49)

Lines 164-167 state this association as follows

"However, there was no association between TFT and severity of illness in patients with different severity of the illness and no differences in TFT between those who needed ICU admission due to severe disease and those who were treated in the general ward."

Answer: This was deleted (line 166-169) and a new statement was added (page 12, line 245-248)

These lines are alluding to a conclusion on this matter based on their study which is problematic and not supported by their data.

I recommend that authors state instead that their study was not adequately powered to detect an association between severity of COVID and TFTs given the various limitations of the study (skewed



data, only n=2 in severity D group, inadequate/heterogeneous follow-up data and others) as stated in text by authors. These sections should be revised to avoid referring to any of the above-mentioned conclusions.

Answer: Thank you for your excellent observations. We have adjusted the text in the abstract and the discussion section to reflect the fact that the study is not powered enough to assess an association between COVID-19 and TFTs as recommended by the reviewer (see above).

----- *End of Review Comments* -----