

Peer Review File

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Reviewer A

Comment 1: ABSTRACT

- please, include sample size in the Method section instead results..
- include a general sentence about statistical main test.

Reply 1: Thank you for this point. In the Method section, we have added the sample size and statistical analyses with the following sentence: “The sample size was calculated, and logistic regression was used to analyze the association”.

Changes in the text: The sample size was calculated, and logistic regression was used to analyze the association (Page 2, Line 44-45)

Comment 2: INTRODUCTION and DISCUSSION section:

- please, improve rationally and discussion more in depth with other studies.
- include more references about this topic.

Reply 2: We have reviewed some relating studies as your suggestion and included in our revised manuscript. The following sentences have been added in the discussion section: “Compared to patients hospitalized ...” and “Also, further studies ...”. All added references were rearranged as appropriate.

Changes in the text: Compared to patients hospitalized for non-COVID-19 conditions, the number of participants with major depression in our study was comparable; meanwhile, the prevalence of generalized anxiety disorder was lower.^{25,26} However, the prevalence of mental problems among hospitalized patients was varied regarding each disease severity or its impact on quality of life. The study about ED prevalence during hospitalization was lacking. Many previous studies reported the number of ED in patients with stable and chronic diseases, which depended on different diagnoses (38.6-82%).²⁷⁻³¹ (Page 8 Line 199-204)

Also, further studies focusing the management and its accessibility are still needed to alleviate the impact of COVID-19 on men’s health.³³ (Page 8 Line 218-219)

Reviewer B

Major

Comment 1: The lack of a control group of any kind significantly limits interpretation of this data. What is the incidence of MDD or GAD in hospitalized patients in general? The incidence of ED in hospitalized men regardless of the etiology?

Reply 1: Thank you for this important consideration. We have added some studies about MDD and GAD prevalence among non COVID-19 hospitalized patients and ED in other medical conditions. Our results were comparable with the data found in previous studies which were varied according to the diagnosis or severity. References have been rearranged as appropriate.

Changes in the text: Compared to patients hospitalized for non-COVID-19 conditions, the number of participants with major depression in our study was comparable;

meanwhile, the prevalence of generalized anxiety disorder was lower.^{25,26} However, the prevalence of mental problems among hospitalized patients was varied regarding each disease severity or its impact on quality of life. The study about ED prevalence during hospitalization was lacking. Many previous studies reported the number of ED in patients with stable and chronic diseases, which depended on different diagnoses (38.6-82%).²⁷⁻³¹ (Page 8 Line 199-204)

Comment 2: This is a study of mental health and ED in hospitalized patients. None of this data is directly attributable to COVID-19 itself. Sick patients admitted to the hospital have diminished sexual drive and erections regardless of the underlying etiology. To make this assertion, a population of men of similar age admitted with non-cardiovascular non-COVID medical problems should be queried about mental health and ED.

Reply 2: Thank you for this point. Since related studies were restricted, ED and mental problems were examined with the limitation of age and diagnosis matching. However, we have reviewed the mental problems among hospitalized patients and included in the discussion section.

Changes in the text: Compared to patients hospitalized for non-COVID-19 conditions, the number of participants with major depression in our study was comparable; meanwhile, the prevalence of generalized anxiety disorder was lower.^{25,26} However, the prevalence of mental problems among hospitalized patients was varied regarding each disease severity or its impact on quality of life. The study about ED prevalence during hospitalization was lacking. Many previous studies reported the number of ED in patients with stable and chronic diseases, which depended on different diagnoses (38.6-82%).²⁷⁻³¹ (Page 8 Line 199-204)

Minor

Comment 3: How many men were intubated? On BiPAP? On NC?

Reply 3: Thank you for this point. None of our participants was intubated and the number of those receiving BiPAP or NC was clarified in the result section.

Changes in the text: Oxygen supplement via nasal oxygen cannula was provided for 20 participants. Regarding the severity of respiratory difficulties, 1 and 4 received an additional helmet noninvasive ventilation and high-flow nasal oxygen cannula, respectively. (Page 6 Line 139-141)

Comment 4: Why were some men admitted with asymptomatic disease? What other admitting diagnoses were present?

Reply 4: According to the policy of The Ministry of Health of Thailand, all individuals with positive COVID-19 result were hospitalized whether they were symptomatic or asymptomatic.

Changes in the text: -

Comment 5: Why were 469 men excluded? Provide exclusion criteria reasoning in supplemental table or describe in text

Reply 5: Thank you for this important point. We excluded patients who were medically unstable, severe medical illness, severe psychological illness and sexually inactive. We have provided the figure illustrating the study protocol (Page 5 Line 128, Page 12).

Changes in the text: The figure 1 has been added. (Page 5 Line 128, Page 12)

Comment 6: Why did most patients still have normal morning erections?

Reply 6: Normal morning erection could represent an intact erection capacity. We believed that the potential etiology of ED among our participants was psychological and mentioned this in the discussion section at Page 7 Line 180-183.

Changes in the text: -

Comment 7: Was this study conducted on patients still admitted to the hospital with active COVID? The timeline of this study is not well described

Reply 7: All participants were hospitalized for COVID-19 at one university hospital in Bangkok during May to July 2021. Even though the study period was quite short, the total number of participants was greater than the calculated sample size, based on previous studies. We have now clarified the power calculation in the method section.

Changes in the text: The sample size was calculated based on prior studies and required a total sample of seventy-eight. (Page 4 Line 95-96)

Comment 8: Line 124 – what is “mild to moderate (3.9%) severity” mean? How many men had severe ED?

Reply 8: None of our participants had severe ED, and mild to moderate severity was graded according to the IIEF-5, which was mentioned in the method section (Page 4 Line 98-101). We have added this sentence according to your suggestion: “None of the participants had severe ED”.

Changes in the text: None of the participants had severe ED. (Page 5 Line 134)

Comment 9: The assertion that hormonal levels could not be checked in the acute setting seems unlikely – I imagine most of these patients had routine blood draws, and a hormone panel could be added on.

Reply 9: Thank you for your comment. Firstly, since most participants were asymptomatic or had mild symptoms, they did not receive any laboratory test except the COVID-19 nasal swab for PCR. Secondly, our research had no financial support, and the hormonal investigation was expensive in our country. Thus, we could not assess and report the hormonal level in our study.

Changes in the text: -

Comment 10: Did these patients recover after admission? Was any follow up performed?

Reply 10: All participants have recovered from COVID-19, but the recovery of ED has not been followed. However, we planned to follow the ED three months after discharge, as discussed in the discussion section.

Changes in the text: -

Comment 11: What power calculation was done to determine sample size (line 86)?

Reply 11: Thank you for this point. We have added the sample size, in the method section, which was calculated from the previous study by estimating an infinite population proportion formula.

Changes in the text: The sample size was calculated based on prior studies and required a total sample of seventy-eight. (Page 4 Line 95-96)

Comment 12: Table 2 stats should be shown by “no ED” and “ED” rather than total and ED. Furthermore, why did 82% of asymptomatic men have ED, which is more than the 70% of the presumably sicker patients with pneumonia. The table is not presented in an intuitive way and should be re-designed.

Reply 12: The purpose of Table 2 was to display the COVID-19 factors of all participants and their association with ED. We believed that the lower number explained the higher proportion of ED among participants with relatively mild symptoms in an asymptomatic subgroup. However, the statistical analyses showed no significant association between the COVID-19 severity and ED. We have added the ‘non-ED’ column as your suggestion and remained the ‘total column’ to portray the overall COVID-19 aspects of our participants.

Changes in the text: The non ED column has been added. (Page 6 Line 136, Page 14)

Reviewer C

Comment 1: The relatively short time frame and number of patients.

Reply 1: Thank you for your comment. All participants were hospitalized for COVID-19 at one university hospital in Bangkok during May to July 2021. Even though the study period was quite short, the total number of participants was greater than the calculated sample size, based on previous studies. We have now clarified the power calculation in the method section.

Changes in the text: The sample size was calculated based on prior studies and required a total sample of seventy-eight. (Page 4 Line 95-96)

Comment 2: Definition of sexual active is vague. The lack of comparative arm (e.g. compared to non-Covid) is an issue.

Reply 2: Thank you for your suggestion. We have added the definition of sexually active in the method section and an additional figure, which illustrated the study protocol. Our study reported the prevalence of ED among Thai patients with COVID-19. We also compared our result with other previous studies examining the ED prevalence in non COVID-19 in the discussion section.

Changes in the text:

- defined as self-reported having sexual intercourse in recent two weeks (Page 4 Line 86-87)

- The figure 1 has been added. (Page 5 Line 128, Page 12)

Comment 3: Need to provide more information about the exact status of COVID in the city (is there a new COVID wave?) and whether any imposed social measures affect other domains such as employment and finances resulting in poor mental health status and hence, the lack of interest in sexual intimacy?

Reply 3: Thank you for this point. The exact status and impact of COVID-19 could precisely explain social burdens, which directly affected mental issues. However, the updated data on COVID-19 consequences and such problems in our study location, Bangkok, during our study period was limited. We then mentioned the association between the COVID-19 impact and mental difficulties in Thailand from one related study in the discussion section. (Page 8 Line 193-196)

Changes in the text: -

Comment 4: Was there any other objective measures of ED performed (e.g. total testosterone, penile colour Duplex U/S etc)?

Reply 4: Most participants were asymptomatic or had mild symptoms, they did not receive any laboratory test except the COVID-19 nasal swab for PCR. Specific investigations were not done due to the risk of COVID-19 transmission. We have mentioned this in the discussion section. (Page 8 Line 210-214)

Changes in the text: -

Comment 5: Did psychological intervention improve the state of ED?

Reply 5: Thank you for this point. The efficacy of psychological intervention in our participants was still questionable. The future study should focus on ED and its association, especially the mental health issues, after discharge from a hospital. Differences in the number of mental problems and the linkage with ED could emphasize the role of psychological intervention in COVID-19 survivors. We have mentioned the suggestion for further study in the discussion section. (Page 8 Line 217-219)

Changes in the text: Also, further studies focusing the management and its accessibility are still needed to alleviate the impact of COVID-19 on men's health.³³

Reviewer D

Comment 1: This is an interesting manuscript given the burgeoning literature regarding COVID-19 and ED. This contributes to the literature despite its limitations. The conclusion isn't new in terms of the mental health associations with ED but is still a worthwhile study.

Reply 1: We appreciate for your kind consideration of our manuscript and the comments.

Reviewer E

Comment 1: The authors' group excluded 469 patients according to the criteria. Many cases were excluded by criteria of this study, and I assumed that the severe illness is the cause of this exclusion. The protocol of this study is unclear, so you need to

clarify exactly study protocol and please provide some kinds of Figure which indicate study protocol.

Reply 1: Thank you for this important point. We excluded patients who were medically unstable, severe medical illness, severe psychological illness and sexually inactive. We have provided the figure illustrating the study protocol.

Changes in the text: The figure 1 has been added. (Page 5 Line 128, Page 12)

Comment 2: The most interesting point of this study is the relationship between Covid-19 infection and ED. Add an additional evaluation to the patient with non-Covid-19 infection to help focus the reader for the discussion of this effect.

Reply 2: Thank you for this important consideration. We have added some related studies. Our results were comparable with the data among non-COVID-19 patients found in previous studies which were varied according to the diagnosis or severity. References have been rearranged as appropriate.

Changes in the text: Compared to patients hospitalized for non-COVID-19 conditions, the number of participants with major depression in our study was comparable; meanwhile, the prevalence of generalized anxiety disorder was lower.^{25,26} However, the prevalence of mental problems among hospitalized patients was varied regarding each disease severity or its impact on quality of life. The study about ED prevalence during hospitalization was lacking. Many previous studies reported the number of ED in patients with stable and chronic diseases, which depended on different diagnoses (38.6-82%).²⁷⁻³¹ (Page 8 Line 199-204)

Comment 3: The author investigated the relation with history of alcohol and nicotine use. History of PDE5 inhibitors medication is also important in the consideration of ED. Additional explanation of the prevalence of PDE5 inhibitor medication should be provided.

Reply 3: Thank you for this point. Only six participants had history of PDE5 inhibitor use. We have added this in the result section.

Changes in the text: Previous use of ED medications was reported in 6 participants. (Page 5 Line 131-132)

Comment 4: It seems that the influence of Covid-19 infection on ED will be the most interesting point for readers. Although recall bias was described as a limitation of this study, you need to develop this idea further and explain the sexual function before Covid-19 infection.

Reply 4: Thank you for your suggestion. Recall bias could be found in every tool used in our study; consequently, all measured outcomes were affected and might present results under a similar condition. Responders might reply mainly their recent periods when they were in their initial phase of COVID-19 infection. We have added this in the study limitation.

Changes in the text: All questionnaires could also be influenced by recall bias; thus the responders might reply based on their recent periods.³² However, it was beneficial

in terms of the results that could better represent the status of each individual during his acute illness of COVID-19 infection. (Page 8 Line 214-217)

Reviewer F

Comment 1: Very well done study. The results are well described and easy to understand.

Reply 1: We appreciate for your kind consideration of our manuscript and the comments.

Reviewer G

Comment 1: Overall, reporting rates of ED in a hospitalized population may not reflect true erectile function, and does not have useful clinical application. These are acutely ill individuals with unknown baselines and unknown erectile function after recovery.

Reply 1: Thank you for this important point. The erectile function after recovery was still questionable. We have mentioned this in the discussion section about the suggestion for further study. (Page 8 Line 217-219)

Changes in the text: -

Comment 2: Table 1 presents two columns that compare ED vs Non-ED patients which is not a comparison that helps to answer the primary question. To look at the potential association between Covid and ED, the two groups to compare should be hospitalized COVID patients and hospitalized COVID-negative patients.

Reply 2: Thank you for your comment. Our primary question was to identify the prevalence of ED among Thai patients with COVID-19. We then collected the participants from COVID-19 patients and categorized them into two groups, as reported in Table 1. Comparing ED vs Non-ED could represent the association between having ED and other variables, which was our secondary research question.

Changes in the text: -

Comment 3: What were the reasons for excluding so many individuals? The exclusion criteria was not very specific and only mentioned severe medical illness and mental illness. Of the excluded individuals, how many were for severe medical illness versus mental illness?

Reply 3: Thank you for this important point. We excluded patients who were medically unstable, severe medical illness, severe psychological illness and sexually inactive. We have provided the figure illustrating the study protocol.

Changes in the text: The figure 1 has been added. (Page 5 Line 128, Page 12)

Comment 4: It'd be more interesting to look at whether the ED percentage and severity was different among those hospitalized with COVID-19 who were vaccinated versus unvaccinated.

Reply 4: Thank you for the suggestion. We have mentioned being vaccinated as one variable, and its association with having ED was not statistically significant. Analyses

with ED severity was limited by the number of participants in each subgroup.
The *P* value of this association was reported in Table 1. (Page 5 Line 130, 133-135/
Page 13)

Changes in the text: -