

Peer Review File

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Reviewer A

This is a well-planned study. The organizational effort the investigators have invested in order to better implement an only seemingly simple procedure shines through the lines.

The importance of APP came to the fore in a global emergency situation with a flow of patients to non-ICU departments with low oxygen saturations that were previously unimaginable outside the ICU. The dramatic situations of the pandemic became significantly scarcer, but COVID-19 remains with us. The credit of the authors of this study is to realize that the fine-tuning of the correct treatment of COVID-19 is still to be established, even after the crisis is over, and to promote efforts to better understand optimal treatment of COVID-19.

What is not yet sufficiently clear from the article is the practical applicability of the findings, although the results the authors found would allow for this. Reading between the lines, we find important results, the emphasis of which would take us forward in this regard as well.

Therefore, I accept the article with recommendations for the following major additions:

1) Specify the target population:

The Abstract has to clearly mention the disease severity of patients included in this study. The information included in lines 96 and 97 - that the patients in this study all required oxygen supplementation and had positive X-ray findings - needs to appear in the Abstract too.

For ex.: in the Abstract at lines 44-46, amend:

"Patients with COVID-19, all hospitalized with positive X-ray findings and oxygen supplementation requirement, in the Respiratory Step-Down Unit of ..."

Reply: Thank you very much for your suggestion. We have added the disease severity of patients in the Abstract.

Changes in the text: see Page 2, line 45-46.

2) The results of this study highlight the importance of Timing and Training for these patients. I think this is the most important added value of this study.

Please do highlight this more:

- Timing: your findings show that

Patients with higher ADL demonstrate less APP duration - these are the patients who are physically active, do not feel that sick (yet?) - for them, APP is probably too early (they do not cooperate because they do not feel the need to).

Patients with higher RR demonstrate less APP duration - high RR is one of the principal signs of worsening COVID-19, - for them, APP is probably too late already (they can not cooperate even if they want to).

... Consequently, the main results of this study appear suitable for determining the most favorable time window for APP intervention during the course of the COVID-19 disease.

- Training:

One of the most important messages of the article is that the efficiency of the APP (patients' willingness) can be increased with the pro-activity and expertise of the staff.

Since the main findings relevant for clinical practice are related to Timing and Training, please emphasize this more! Preferably in the Title, and certainly in the Abstract, and in the Highlights.

In the Title, for ex.: "Implementation of awake prone positioning in patients with COVID-19: importance of timing and training to elevate oxygen saturation. A single center prospective observational study"

or "Implementation of awake prone positioning in patients with COVID-19: timing and training seem key factors to elevate oxygen saturation. A single center prospective observational study"

In the Abstract: line 59, change "and" to "but", and amend lines 58-60, amend this sentence for ex.: "Patients with lower tolerance to ADL but lower RRs were those to demonstrate a longer duration of prone positioning. This is pointing towards establishing the most favorable time window for APP during the course of COVID-19: after the activities of daily living have already decreased, but before significant tachypnea has appeared"

In the Highlights: line 414, be more specific, do not just write "vital signs". What you found is more important and more specific than this. You could write for ex.: "Decreased activities of daily living were associated with better-, higher respiratory rates with lower compliance with APP and the resulting improvement in oxygen saturation. The findings seem to delineate the optimal timing for APP, when used for slowing COVID-19 progression: it is after the ability of daily living has decreased, but before significant tachypnea appears"

Reply: Thank you very much for your valuable comments. We have revised the title, abstract and the highlights according to your suggestions.

Changes in the text: see Page 1, line 2-3; Page 2, line 59-63; Page 14, line 451-454.

3) To facilitate practical application of the findings, please add a Check list and preferably a Figure, to summarize and illustrate the necessary preparations and correct technique to implement APP.

List all that is suggested by the authors for successful APP implementation, based on their collected experience. (You can do this as a printable Supplementary Material too, for use at the bedside).

For example,

In the check list: list what you think the patient should be explained before the procedure, what are main reasons of non-compliance and how to solve them, what are the most common technical obstacles and how to solve them at the bedside, etc.

In the illustration: show the correct and incorrect position of the pillow, etc.█

Of course, such printable check-list and illustration has to include the warning that its preliminary recommendations are based on the preliminary results of the first observational studies, and that the correct application of APP requires further investigations.

Reply: Thank you very much for your suggestion. We have added the APP Check list.

Changes in the text: see Page 12, line 404-405; Page 20-21, line 563-565.

* * *

Furthermore, I recommend the following important amendments:

- line 169, you write "8 patients died". Please add a line explaining why these patients were not transferred to ICU, how the decision was made.

Reply: Thank you very much for your suggestion. We have added the explanation, they refused to be intubated for further treatment.

Changes in the text: see Page 6, line 181.

- line 101 you write patients unable to comply were excluded from the study. If possible, can you specify how many? How many patients were screened, before getting to the 150 who were included? This is an important question because it would help to estimate the extent to which APP is difficult to implement in everyday practice.

Reply: Thanks for your suggestion. We have added the data. "677 patients were admitted to Respiratory Step-Down Unit of the Peking University Third Hospital between January 6th, 2023, and January 20th, 2023, 423 of whom met the indication for APP."

Changes in the text: see Page 5, line 165-167.

* * *

Finally, I suggest the following minor corrections:

- line 50: please amend with the words "one hour after APP", since the saturations were recorded one hour after the end of APP (as you explain in line 179); so at line 50 it is "...showed an improvement in oxygen saturation one hour after APP."

- line 77: instead of "provides", it is "recommends"

- line 155: please amend the word "initial" since saturations were not followed up; so it is "initial improvement in SpO2"

Reply: Thank you for your suggestions on the revision of the article, the above content has been modified.

Changes in the text: see Page 2, line 51; Page 3, line 80; Page 5, line 160.

Reviewer B

The authors have summarized their experience in awake prone positioning for non-severe COVID-19 patients. They have demonstrated some factors associated with improvement in SpO2 and factors associated with increased duration of prone positioning

In fact, the effect of awake prone positioning has well been studied in several randomized trials. However, this study looks meaningful in that they showed their experience in real clinical setting.

I think, however, that the clinical significance of factors associated with improvement in oxygenation (SpO₂ and HR) may be not so clear. This is because the improvement of oxygenation was actually so small (95% -> 97%). This little difference may not result in improvement in clinical outcome, which authors have mentioned as well.

I think the authors may have to focus more on the factors associated with duration of prone positioning, because these findings look more novel findings. I recommend this finding should be more focused in the manuscript, instead of factors associated with improvement of oxygenation.

Reply: Thank you very much for your suggestion. We have revised the title to “Importance of timing and training to implement awake prone positioning in patients with COVID-19: A single-center prospective observational study”, reflect the importance of time and training. We also revised the abstract and highlights to statement the time window for APP intervention during the course of the COVID-19 disease in the study. “Decreased activities of daily living were associated with better-, higher respiratory rates with lower compliance with APP and the resulting improvement in oxygen saturation. The findings seem to delineate the optimal timing for APP, when used for slowing COVID-19 progression: it is after the ability of daily living has decreased, but before significant tachypnea appears.”

Changes in the text: see Page 1, line 2-3; Page 2, line 59-63; Page 14, line 451-454.

Reviewer C

This is an observational study aimed to explore the factors that influenced the APP implementation. The authors also conducted qualitative interview. My comments are shown below:

Major:

1. Unclear aim: the authors claimed that their aim was to explore the factors influencing the implementation of APP, but they spent lots of efforts to evaluate the influential factors of SpO₂ improvement during APP.

Reply: Thank you very much for your question. We have modified the Background, Conclusions and the highlight box to highlight the aim. “Background: Awake prone positioning (APP) is broadly implemented in patients with SARS-CoV-2 related disease (COVID-19) admitted to hospital with severe respiratory distress syndrome. This prospective observational study aimed to explore the factors influencing the implementation of APP in patients with acute respiratory failure due to COVID-19.” “Conclusions: The APP ventilation technique effectively improved the SpO₂ in patients with acute respiratory failure due to COVID-19. Patients with lower tolerance to ADL but lower RRs were those to demonstrate a longer duration of prone

positioning. This is pointing towards establishing the most favorable time window for APP during the course of COVID-19: after the activities of daily living have already decreased, but before significant tachypnea has appeared.” “Decreased activities of daily living were associated with better-, higher respiratory rates with lower compliance with APP and the resulting improvement in oxygen saturation. The findings seem to delineate the optimal timing for APP, when used for slowing COVID-19 progression: it is after the ability of daily living has decreased, but before significant tachypnea appears.”

Changes in the text: see Page 2, line 40-44; Page 2, line 59-63; Page 14, line 451-454.

2. The validity of the outcome variable SpO₂: it can be easily affected by the oxygen device or FIO₂ utilized. second, based on the SpO₂-PaO₂ curve, SpO₂ can be affected by the numbers as well, for example, if the SpO₂ is 98%, it is difficult to improve the SpO₂. In contrast, if the SpO₂ is 88%, it is easy to improve the SpO₂.

Reply: Thank you very much for your suggestion. SpO₂ is affected by many factors, and it is difficult to raise SpO₂ on higher level if the SpO₂ is above 95%. Other outcome measures, such as PaO₂ may be more accuracy. However, not all of the patients have this result in this study since it needs blood gas analysis which is invasive, complex and cost.

Changes in the text: No change.

3. Ethical concerns: Is this study a prospective study? if it is the former, did they consent the patients? Did they register this study?

Reply: Thank you very much for your question. This study was a prospective study, and all enrolled patients signed informed consent. This study was approved by the Institutional Ethical Review Board of Peking University Third Hospital (No. 2023-088-01).

Changes in the text: No change.

3. Insufficient literature review: there are several studies published on the influential factors of APP adherence, the authors did not sufficiently compare and contrast their findings with others.

Reply: Thank you very much for your suggestion. We have added studies published on the influential factors of APP adherence.

Changes in the text: see Page 12, line 374-377, 394-398; Page 16, line 514-516; 423-425.

Minor:

1. Abstract:

a. “Several aspects of APP are controversial, in term of safety and efficacy”: incorrect statement and irrelevant to the study aim (to explore the factors influencing the implementation of APP)

Reply: Thank you very much for your question. We deleted the sentence "Several aspects of APP are controversial, in term of safety and efficacy". and stated “This prospective observational study aimed to explore the factors influencing the implementation of APP in patients with acute respiratory failure due to COVID-19.” in the Abstract.

Changes in the text: see Page 2, line 40-44.

b. “The APP technical steering group”: what did the group do?

Reply: Thank you very much for your question. The APP technical steering group is mainly responsible for the training and assessing of APP technology before nurses start work, and is also responsible for the assisting and guiding the respiratory step-down unit in performing prone positioning.

Changes in the text: No change.

2. The finding of “The APP ventilation technique effectively improved the SpO₂ in patients with acute respiratory failure due to COVID-19.” is broadly accepted, it is not new.

Reply: Thank you very much for your question. “The APP ventilation technique effectively improved the SpO₂ in patients with acute respiratory failure due to COVID-19.” is broadly accepted, it is not new, it is just part of the result. The new is “Decreased activities of daily living were associated with better-, higher respiratory rates with lower compliance with APP and the resulting improvement in oxygen saturation. The findings seem to delineate the optimal timing for APP, when used for slowing COVID-19 progression: it is after the ability of daily living has decreased, but before significant tachypnea appears.”

Changes in the text: see Page 14, line 451-454.

3. “Logistic regression analysis was used to determine the associated factors of the improvement in SpO₂ after prone positioning”: how to determine “improvement”? improved by 1% or more would be considered as “improvement”?

Reply: Thank you very much for your question, improved by 1% or more would be considered as “improvement”. SpO₂ improvement refers to the increase of SpO₂ 1 hour after APP, while the SpO₂ nonimprovement refers to no change or decrease of SpO₂. We have added the statement.

Changes in the text: see Page 6, line 191.

4. “2 patients received nasal cannula oxygen, 4 patients received oxygen storage masks, and 2 patients received bilevel positive airway pressure (BiPAP) ventilation.”: what about the rest of 126 patients? Didn’t they use oxygen?

Reply: Thank you very much for your question. “2 patients received nasal cannula oxygen, 4 patients received oxygen storage masks, and 2 patients received bilevel positive airway pressure (BiPAP) ventilation.” It was oxygen therapy for 8 patients who died. We've added oxygen therapy for 134 patients, “112 patients received nasal cannula oxygen, 8 patients received oxygen storage masks, 8 patients received high flow nasal cannula, and 6 patients received bilevel positive airway pressure (BiPAP) ventilation.”

Changes in the text: see Page 6, line 175-177.

5. “Two out of the 134 included patients developed complications during prone positioning: one developed facial edema while the other developed scrotal edema. Consequently, they suspended the APP .”: how long did the two patients prone?

Reply: Thank you very much for your question. We added the duration of APP treatment in the event of edema. “Two out of the 134 included patients developed complications during prone

positioning: one developed facial edema (APP treatment 5.5h) while the other developed scrotal edema (APP treatment 4h). Consequently, they suspended the APP.”

Changes in the text: see Page 8, line 244-246.

5. Figure 1 is confusing: 1) is the APP treatment time the average time per patient or total time for all patients? 2) Why did the APP time increase while the number of the patients receiving APP dropped?

Reply: Thank you very much for your question. APP treatment time is the average time per patient. We have added the reason for the number of the patients receiving APP dropped. “The number of participants gradually decreased as patients' conditions changed.”

Changes in the text: see Page 7, line 236-238.