

Peer Review File

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Reviewer A

In this study, the authors aimed to investigate the uptake of the COVID-19 booster vaccine in COPD. In addition, the predictors of booster vaccination uptake were evaluated. My suggestions for each section are as follows:

Major comments

1. In my opinion, if we want to understand what the reasons are that nudge people toward getting a booster dose (or not), we need to identify some aspects, including perceptions of infection risk, attitudes towards the effectiveness of the booster vaccine, vaccine knowledge, the side-effects after receiving the former two doses, etc. But I fail to find information about patients' attitudes, motivations, or beliefs toward COVID-19 booster vaccination. This perhaps could be enclosed in the study limitation section.

Answer: Thank You very much, the primary objective of our study was to assess the overall vaccination coverage against COVID-19 among COPD patients - as the vaccination coverage of the general population in Hungary is very low, the study of specific (e.g. COPD) patient populations is of scientific value in itself. As we saw a very large discrepancy compared to the average population, we performed the analysis described in this article based on the available data. Thank You very much for your valuable comment, we did not ask about beliefs, attitudes, and side effects unfortunately in this research. Thank You, we have added the limitations.

2. The data from logistic regression analysis in the Abstract, Results, as well as in the Discussion is inconsistent with the results presented in Table 5. For example, I can't find these variables, such as "more severe COPD (line 56)", "patients with more severe GOLD stage (line 253)", and "place of residence and quality of life (line 269)", influenced the uptake of booster vaccination from Table 5. This should be explained for clarity.

Answer: Thank You, Table 5 includes quality of life questionnaires (CAT, mMRC), GOLD AB/CD stages, and residence classification: region of living: central, eastern, western.

3. I found the Method section in this paper is nearly the same as your previous publication (<https://doi.org/10.1016/j.vaccine.2022.11.020>). Please paraphrase, instead of directly using the same wording or simple word switching. I suggest rewriting the whole section.

Answer: Thank You, we have rewritten the methodology, and confirmed by reference.

Specific comments

Title

1. I would suggest a more precise title. "Booster dose" is not specific. The authors should clearly indicate "the initial booster doses" or "the third booster doses" to avoid misinterpretation as the additional booster doses or the fourth dose.

Answer: Thank You, we have corrected the title of the manuscript.

Abstract

1. Line 59, how did the authors define “the target”?
2. Abbreviations should be defined at first mention, such as COPD, CAT, and mMRC in the Abstract.
3. It was inconsistently described the periods of recruitment in the Abstract and the main text. Please clarify the correct date.
4. Line 50, “CAT: 16 (11-21)”, but in Table 1, it was “CAT: 15 (11-21)” instead. All numbers have to be checked thoroughly and adapted accordingly.
5. Lines 53-55, “The factors that were most associated with higher COVID-19 vaccine booster dose uptake were older age (OR: 1.06; 95% CI: 1.04-1.08), male gender (OR: 0.74; 95% CI: 0.57-0.96), absence of previous COVID-19 infection (OR: 0.34; 95% CI: 0.23-0.51)”, this information was wrong. The factors “male gender and absence of previous COVID-19 infection” (associated with lower) and “older age”(associated with higher) should be described separately.
6. The significant findings were not limited to CAT, mMRC, and the number of moderate exacerbations. Please consider revising the statements from lines 49 to line 52.

Answer: Thank You, we have corrected the manuscript.

Lines 53-55, “The factors that were most associated with higher COVID-19 vaccine booster dose uptake were older age (OR: 1.06; 95% CI: 1.04-1.08), male gender (OR: 0.74; 95% CI: 0.57-0.96), absence of previous COVID-19 infection (OR: 0.34; 95% CI: 0.23-0.51)”, this information is correct, so we have not changed this in the manuscript. The exact results are shown in both Table 1 and Table 5, with male gender increasing vaccine uptake, and the absence of previous COVID-19 infection also increases vaccine uptake.

Introduction

1. It’s stated that the third and fourth booster vaccines have a substantial impact on reducing severe disease and death. The authors would better report whether additional booster doses (the fourth dose) are currently being offered by Hungary. If so, please state why they focus on the third one. In addition, the knowledge gaps and novelty of the study are not clear in the Introduction. How about the injection rate, the influence factors of uptake of booster vaccines in COPD patients in Hungary?

Answer: There is also a medical proposal to include the 4th vaccine, but there is not as much political pressure on people and patients to include it as there was with the 3rd COVID-19 vaccine. When the research was done, vaccine 4 was not yet available to the public and patients. In addition, we saw in the first analysis of the study (article by Monika Fekete et al. <https://doi.org/10.1016/j.vaccine.2022.11.020>) that after the first two vaccines are taken up, the willingness to vaccinate drops tremendously, so to investigate what socioeconomic factors influence this in Hungary is a very important scientific question for us.

2. Line 92, “According to a CDC study” is weird. There are two references (Ref. 9,10). Please modify.

Answer: Thank You, we have corrected it.

3. In the final paragraph of the Introduction, the authors only emphasized the knowledge, or misconceptions about vaccination, which is probably not the main topic of this paper. The authors could add a few new sentences to describe physiological determinants or

sociodemographic factors of acceptance of the booster doses of COVID-19 vaccination.

Answer: Thank you for your valuable comment, I have added the information to the introduction.

Methods

1. Lines 131-132, patients are enrolled from outpatient's pulmonology clinics, please also state whether these are from community hospital, tertiary hospital, or secondary hospital? Because this also determines the representativeness of the data.
2. The statements in lines 133- 135 are difficult to understand. I'm not talking about the grammar issue, but about what the "three main stages "and "interim analysis "have to do with this study.
3. In your previous study (as mentioned above) ---with the same docket number and registration number, which I assume are the same investigation, it's stated that "1,511 patients were included". Why in this study, only 1,510 patients were left. It should be explained for clarity.
4. Line 155, "current heavy smoker never smoked or quit smoking", missing use of a comma. Please correct this to "current heavy smoker, never smoked or quit smoking".
5. There was no statistical definition of the sample size. Would you please explain how the sample size was determined?
6. Line 196, regarding the definition of COVID-19 infection, why are asymptomatic cases excluded?
7. It is mentioned that no missing data in the study in the STROBE checklist. Please highlight this point in the main text, too. In addition, it looked to me that missing data is inevitable with such a large sample size. Can the authors report the efforts you take to address this issue?
8. Line 206, it's preferable to use "Shapiro-Wilk test", rather than "Sapphiro-Wilk test". The authors report the alpha level ($p < 0.05$) that defines statistical significance and should also state whether tests were one- or two-tailed.
9. It should be stated the criteria to be included in multivariable logistic regression analysis. For the authors' reference, "Statistically significant factors ($P < 0.05$ or $P < 0.02$) in univariate analysis were subsequently entered into the multivariate logistic regression model".

Answer:

Thank You, the patients are from a community hospital, we have corrected the manuscript.

Thank You, lines 133- 135 have been removed from the manuscript.

In total, doctors recruited patients in three groups, which differed in time. Interim means that we conducted our analysis when all centers in the first group had finished enrolling patients.

Thank You, yes, 1510 patients were left in the analysis, we have corrected the manuscript, the changes are marked.

Thank You, asymptomatic COVID cases were not excluded from the study, we have corrected the manuscript.

Thank You, we have corrected the "Shapiro-Wilk test" and the criteria to be included in the multivariate logistic regression analysis. There was no prior sample element calculation and estimation, because COPD patients at the outpatient clinic were included based on the inclusion criteria listed. The study contained a minimal amount of missing data, therefore no data input method was done. A more detailed statistical analysis, multiple logistic regression was executed which was adjusted for potential confounders, which was carried out on complete records. All

statistical tests were two-sided. We adjusted the multiple logistic regression for many confounding factors available in the dataset, such as: gender, age, place of residence, smoking status, etc. (see Table 5). It is possible that during the univariate analysis no significant relationship can be found, however an effect might exist, it can happen due to confounding, which might distort the relationship between the explanatory variables and the outcome, that is why a relatively complex multiple model was executed. The p-values in the table 1 refer to the heterogeneity differences observed in the different strata of the explanatory variables regarding vaccination uptake groups. In the case of continuous variables the median values were compared between the two groups analyzed.

Results

1. The authors only present the number of participants in the FINAL stage. We suggest the authors use a flow diagram to report the number of participants at each stage, from the selection of potentially eligible ones to the final included ones, and with reasons for exclusion.
2. Table 1 is hard to read. For example, what does the p stand for? The difference between the two groups or the difference between man and woman in the group receiving a booster dose vaccine?
3. Lines 191-195, acute worsening, severe and moderate exacerbation were defined, while in Table 1 only severe and moderate exacerbation were described. Please rectify.
4. Line 224, how could the authors say, “while 86.62% of patients were double vaccinated”, which was not referred to in the paper?
5. For ease of reading, it would include these paragraphs in the Results section with subheadings, such as “sociodemographic and functional features”, “multivariable logistic regression analysis” etc.
6. In the main text, repeating all the results of the tables seems to be unnecessary and makes it difficult to read through. It might be better to highlight some key findings that comply with the objectives, but rather duplicate all findings. Please make the required adjustments in this regard.
7. In Line 245, only SABA was mentioned as statistical significance. What about LABA, ICS and LABA, ABA and LABA and ICS?
8. In the Results section, there just seems to be a p-value attached to some findings. It’s recommended to present key results with precise data and their precisions (e.g. 95% CI), such as the statement in line 253.

Answers: Thank You very much for your valuable comments, all points have been corrected in the results section of the manuscript, marked as shown. Thank You, I have corrected the p-values in the table and in the text according to the author's instructions. In total, one person was excluded from the survey, because we could not confirm with certainty the inclusion of the booster vaccine.

Tables

1. Please adjust the tables with three horizontal lines. Significant results are best displayed in bold, or authors consider using the asterisk (*) for an easier way to check the results.
2. Table 1:
-In line 147, data on “previous history of COVID infection” was collected, but they were not mentioned in Table 1. I suppose the “Covid-19 infection” in Table 1 means “Covid-19 infection

after getting COVID-19 booster dose”, not the previous infection. This should be clarified.
-For the GOLD stage “<0.859, <0.016, <0.621”? Please correct.
-In the annotation, please delete “6MWD: six-minute walking distance; SD: Standard deviation” as they were not mentioned at all.

3. Table 2: Please correct Hypertonia” to hypertension”.

4. Table 4:

-Move up the “Number of visits to health care facilities in the last year” to the second row.
- “Data are presented as frequency and percentage” in the annotation, but the data were indicated as Median [IQR] or Median (range), I guess. Please make sure of it and revise accordingly. For IQR, use bracket “()” uniformly.
-Please define “GP” in the table legend.

Answer: Thank You very much, we have corrected the tables in all points. Men were significantly more likely to receive the COVID-19 first booster vaccine ($p < 0.001$) than women.

Discussion

1. A key point: the author should give a very specific suggestion on how to increase the booster vaccination rate of COPD patients in Hungary compared with other studies. This will reflect the clinical implications of this article.

2. Line 272, “COVID-19 continues to be endemic in the United States, seems out of place here.

3. Some parts of the Discussion section of the manuscript read like the Introduction. For example, the second paragraph of the Discussion illustrates the vaccine effectiveness and importance of taking a booster vaccine. This should therefore either be merged into the Introduction section or removed. Please check again to address similar concerns.

4. The authors have restated the results and described the existing literatures. As a reader, I was hoping to see more discussion on the interpretations of the predictors of booster vaccine uptake in COPD patients and delete the irrelevant discussions such as the smoking rate.

5. Additionally, one more thing about the limitation, the vaccination status, and symptoms were based on patient self-reported data, potentially leading to misclassification.

Answer: Thank You very much, Line 272, “COVID-19 continues to be endemic in the United States” the sentence and section has been deleted from the manuscript.

Other comments

1. Please further revise the manuscript based on the Guidelines for Authors of APM. The author could download the structure template to rearrange the paper’s structure, such as the Highlight box, Introduction, Discussion, Reporting of P values, etc.:
<https://cdn.amegroups.cn/static/public/2.1-Structure%20of%20Original%20Articles-template-V2022.11.4.docx>

2. Please update the STROBE reporting checklist based on the latest version of your article.

Answer: Thank You very much, we have downloaded the structural template and corrected the manuscript, and updated the STROBE checklist. Thank You, I have corrected the p-values in the table and in the text according to the author's instructions.

Reviewer B

First, the title needs to indicate the other focus of this study, factors associated with the uptake

of COVID-19 booster dose.

Answer: Thank You very much, we have changed the title of the manuscript.

Second, the abstract needs some revisions. The background did not indicate the clinical significance of this research focus and what the knowledge gap is in relation to the uptake rate of COVID-19 booster dose and its associated factors. The methods did not describe the inclusion criteria, sampling of subjects, assessment of potential factors, and measurements of the status of uptake rate of COVID-19 booster dose. The results need to clarify who were “others” in the sentence “Compared to patients who were vaccinated three times with the others”. The conclusion needs to provide the target uptake rate and have comments for the clinical implications strictly based on the current findings.

Answer: Thank You very much, we have revised the abstract.

Third, the introduction of the main text needs to review the vaccine hesitance and uptake in patient population including COPD patients and factors associated the uptake of the vaccines. The authors need to further clarify the clinical significance of the current research focus in COPD and analyze the knowledge gaps on the vaccine uptake in COPD.

Answer: Thank You very much, we have revised the introduction.

Fourth, in the methodology of the main text, please describe the sampling of subjects, detailed inclusion criteria, and sample size estimation procedures of this study. My major concerns regarding the methodology are the long survey period of this study, from November 2021 to November 2022, and the poor design of potential factors associated with the uptake. Because the uptake of vaccines was dynamic and different form month to month, so the uptake rate is not convincing in this study. The authors have reviewed relevant papers and described that most associated factors of vaccine uptake were attitudes towards vaccination, beliefs on the efficacy of the vaccines, perceived safety of the vaccines, and worry about the infection of COVID-19, but the authors did not assess any of these factors. The CAT, lung function and BMI, in fact, were not the main factors associated with the uptake. This is a major limitation of this study. Please accurately define “unvaccinated” in this study: did not take the third vaccine or did not take any COVID-19 vaccine? In statistics, please ensure $P < 0.05$ is two-sided and describe the details of multiple logistic regression analysis.

Answer: Thank You very much for the valuable comment, in our research, we wanted to know how many COPD patients in Hungary have taken the 3rd vaccination. We knew that 86.1% of the patients had two vaccinations (see article by Monika Fekete et al. <https://doi.org/10.1016/j.vaccine.2022.11.020>). Other, previous researchers have described the beliefs and attitudes towards vaccination, we did not ask these questions in this study.

Thank You, yes, for the "unvaccinated" in this study: they did not take the third vaccine.

Thank You, we have corrected the methodology and the statistics.

1. Xu B, Zhu Y. A systematic review and meta-analysis of the factors associating the willingness of Chinese community residents to receive COVID-19 vaccine. *Ann Palliat Med.* 2022;11(11):3483-3493. <https://doi.org/10.21037/apm-22-1099>
2. Wang X, Shen M, Zhang Q, et al. A web-based survey of SARS-CoV-2 vaccination and

its adverse effects in Chinese postoperative patients with breast cancer: a cross-sectional study. *Gland Surg.* 2022;11(9):1497-1506. <https://doi.org/10.21037/gs-22-454>

Answer: Thank You very much, these references are also cited in the manuscript.