Peer Review File
Article information: https://dx.doi.org/10.21037/jtd-22-1565

Reviewer A

Major comments:

Comment 1: Most of the introduction seems disconnected from the main objective of the study. Why do we need the prediction model for COVID-19 lung injury? What is the knowledge gap? How will it help future patients?

Reply 1: Thank you for giving us the opportunity to clarify this question. In our opinion, the Introduction follows a classical structure. In the first paragraph, we provide some historical and epidemiological data about the disease. In the second paragraph, we describe its forms of presentation (only a small proportion of patients with this disease require hospitalization) and state that treatments are generally effective, although some long-term effects have been reported. Then, a definition is provided of "post-acute COVID-19 syndrome" and a description is provided of the problems that follow-up of these patients may pose to public health. At the end of the second paragraph, we have introduced a statement about the relevance of being able to estimate which patients are more likely to develop long-term effects, since they could benefit from more specific follow-up programs, which can also be interpreted as a diagnostic hypothesis. Finally, in the third and fourth paragraph, following our line of argument, we expose the objectives of our study. To fulfill the primary objective (determining whether our models identified the patients who ultimately developed sequelae), we first had to identify the sequelae related to the disease.

As stated above, these predictive models may play a relevant role in the identification of patients who will develop long-term sequelae, which will enable early management. This would also help future patients with persistent COVID-19 symptoms.

Comment 2: Was the research carried out in adherence to the TRIPOD checklist?
https://www.equator-network.org/reporting-guidelines/tripod-statement/
https://bmcmedicine.biomedcentral.com/articles/10.1186/s12916-014-0241-z

Reply 2: Thank you for the information provided. We'll follow the TRIPOD checklist.

In this case, the knowledge gap is the lack of understanding of the patients who are more likely to develop respiratory problems and how to identify the patients at a high risk of developing these problems. We have modified the sentence at the end of the second paragraph, as required by the other reviewer to clarify this aspect.

Changes in text 1: "Patients with post-acute COVID-19 syndrome need long-term follow-up. Considering their acquired disability, declined quality of life, and increased use of healthcare resources use, specific health programs should be designed for these patients. Although the prevalence of this syndrome is not high, massive SARS-COV-2 infection may pose a serious public health problem, due to the intensive use of health resources that this syndrome involves. In the light of the inconsistent evidence currently available, it is necessary to develop tools that identify patients at a higher risk of developing lung injury after SARS-CoV-2 hospitalization. The use of these tools would facilitate the development of specific integral follow-up programs from which these patients would benefit". (Page 14, 2nd

paragraph).
Comment 3: The overall hypothesis of the manuscript is not clearly defined. What do the authors intend to do? Is it to develop a model or validate a model?
Reply 3: Thank you for posing this question. At the end of the second paragraph, we included a sentence to formulate the hypothesis that de use of one or several models that estimate the probability that a patient develops long-term sequelae would be useful for COVID-19 patients. We plan to develop a prognostic model that will be tested with series from other hospitals.
Changes in text 2: "it is necessary to develop tools that identify patients at a higher risk of developing lung injury after SARS-CoV-2 hospitalization. The use of these tools would facilitate the development of specific integral follow-up programs from which these patients would benefit". (Page 15, 1st paragraph).

Comment 4: Methods are not clearly described either. No details are given for the design of models. Was there any bootstrapping? How was the data utilized? No information about data distribution into the Training set versus the validation set.
Reply 4: We have re-written the statistical analysis section. We did not split data into training and validation sets. We performed internal validation using bootstrapping techniques but to test optimism as mentioned in the statistical analysis section. Now we hope this section is clearly described.

Comment 5: "In patients with mobility problems, diagnosis of pneumonia was established by transthoracic echocardiogram" I wonder if the authors mean bedside lung ultrasound and not the echocardiogram. The manuscript needs a thorough proofread before peer review or even submission to the journal.
Reply 5: Thank you for your comment, there was a terminological error. The correct term is "lung ultrasound". The manuscript has been revised by a professional scientific translator. We think the text meets standards for submission for peer review.
Changes in the text 4: "In patients with mobility problems, diagnosis of pneumonia was established by lung ultrasound[16]". (Page 16, 1st paragraph).

Comment 6: Line 455: "showed higher mean peaks of inflammatory parameters" do the authors mean "elevated levels of inflammatory markers"? Overall language of the manuscript needs a lot of work. Strongly suggest using English language editing or writing services.
Reply 6: Thank you for your suggestion. The manuscript has been revised by a professional scientific translator. With regard to the expression "Showed higher mean peaks of inflammatory parameters" we meant that we considered the highest value reached by each inpatient for each parameter; then, considering the maximum values reached for each parameter by each patient, we calculated the average maximum value for the totality of patients. Then, we assessed differences in mean maximum values between the group of patients who stayed in a conventional ward and those who stayed in the CCU (Table 1). We corrected the sentence.
Changes in the text 5: "Finally, CCU patients showed higher average of peak values of inflammatory markers". (Page 19, 1st paragraph).

Comment 7: The opening line of the discussion is “Our results reveal that a high proportion of patients hospitalized for COVID-19 have a risk of experiencing persistent respiratory symptoms, deterioration of pulmonary function; changes in functional status; or fibrotic pulmonary lesions on imaging studies a year after infection. PCFS at the initial visit; a history of bronchial asthma; gender; FVC percentage with respect to initial visit; and CCU stay are predictive factors for the development of persistent symptoms and post-COVID-19 fibrotic pulmonary lesions.”
What does that have to do with anything?
Reply 7: Thank you for your comment, which enabled us to improve our manuscript. This first paragraph summarizes the most relevant results obtained, which are thoroughly analyzed in the Discussion section. The first sentence (until “…. a year after infection.”) is related to the first objective of the study, which was “*to identify the persistent pulmonary lesions that long-stay patients developed one year after SARS-COV-2 infection*”. The second sentence (from “PCFS at the initial visit”) describes the variables included in the models to predict the development of pulmonary problems one year after infection. We reformulated the sentence.
Changes in the text 6: “Prognostic factors of persistent respiratory symptoms after COVID-19 include PCFS at the initial visit and history of bronchial asthma. Sex, percentage of FVC with respect to initial visit, and CCU stay are prognostic factors of post-COVID-19 fibrotic pulmonary lesions”. (Page 22, 1st paragraph).

Comment 8: The title of the manuscript and writing do not correlate whatsoever (Title: Predictive models for lung injury one year after COVID-19-related hospitalization: A prospective study.)
Reply 8: In the manuscript, we posited a hypothesis (“the use of these tools would facilitate the development of specific integral follow-up programs from which these patients would benefit”) and defined a set of objectives (“*to identify the persistent pulmonary lesions that long-stay patients developed one year after SARS-COV-2 infection and investigate whether it is possible to estimate the probability to develop persistent respiratory symptoms”)*. Throughout the study, we identify five variables that could help estimate the probability that a patient develops pulmonary lesions one year after infection. Thus, these variables were used to construct two models: Model 1 to predict the occurrence of persistent respiratory symptoms and Model 2 to predict who will develop post-COVID-19 fibrotic pulmonary lesions. These results are discussed and conclusions are drawn in relation to the title and objectives of the study. We hope the new title and writing of the manuscript correctly correlate now, although other aspects are addressed in some parts of the manuscript.
Changes in the text 7: “Development of prognostic models to estimate the probability of lung injury one year after COVID-19-related hospitalization. A prospective study” (1st page, 1st paragraph).

Comment 9: Line 562: “Our prognostic models to identify patients with a higher risk of developing post-COVID-19 fibrotic lesions are based on five parameters”
Authors go back and forth with the use of words like “prediction” and “prognostic” models; they are not interchangeable and mean very different things described elsewhere.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4106488/

https://onlinelibrary.wiley.com/doi/pdf/10.1111/jth.12262
https://www.bmj.com/content/369/bmj.m1328
Reply 9: Thank you. We used the two terms indistinctly, albeit we are aware that prognosis and prediction are not interchangeable. This is a prognostic study aimed at identifying hospitalized patients for Covid-19 who will develop persistent pulmonary lesions in the future. We corrected the terms used.
Changes in the text 8: The term prediction was replaced with prognostic: Page 10, 3rd paragraph; Page 11, 1st paragraph; Page 18, 2nd paragraph; Page 20, 3rd paragraph; Page 22, 2nd paragraph and Page 24, 1st paragraph).

Comment 10: Line 576: limitations; "it is a single-center study without external validation and is based on a small sample of patients" there is NO internal validation either, as per the manuscript. Unclear from the methods section.
Reply 10: Thank you. There are different methods available for internal validation. A frequently used method consists of separating the sample into two parts: training and validation sets. Another method is bootstrapping, which we used to correct overoptimism in our models.

Comment 11: Line 581: Conclusion: "although values prior to SARS-COV-2 infection were not available, the results of this study suggest that a high percentage of COVID-19 hospitalized patients develop pulmonary lesions though with low lung function impact" what does that have to do with the study? That was not the hypothesis or outcome of interest or the title of the study. The title, methods, results, and conclusions are completely disjointed.
Reply 11: Thank you for your observation. As we stated above, for us to be able to construct the prognostic models, we first needed to identify the pulmonary lesions that patients develop in the long term. For this reason, that is the primary objective of the study: "*The objectives of this study were to identify the persistent pulmonary lesions that long-stay patients developed one year after SARS-COV-2 infection"*. Therefore, as that is the primary objective (otherwise we could not construct the models), the first conclusion should correlate with the primary objective. Then, the second conclusion is related to the second objective ("*… and investigsate whether it is possible to estimate the probability that a patient develop persistent respiratory symptoms"*) and is consistent with the new title (*Development of prognostic models to estimate the probability of lung injury one year after COVID-19-related hospitalization. A prospective study*). Otherwise said, to fulfill the primary objective of the study (which explains the title), we first needed to identify the type of pulmonary lesions that patients developed in the long term (another gap of knowledge since it is a recent disease), which is the primary objective (chronologically speaking); the first conclusion addresses the primary objective.

Reviewer B

Comment 1: Authors have performed a valuable prospective study with a substantial number of patients, although it was a single center study. In fact, there have been many other studies to see long-term 1-year sequelae of COVID-19 patients; however, this study has its own

strength in that the authors analyzed two aspects of sequelae (subjective symptom of patients and fibrotic change objectively identified on chest CT), respectively. I have some comments as below.
Reply 1: Thank you for your comments.

Comment 2: Abstract needs clarification in some points. First, the methods section does not have enough information regarding what the authors have actually analyzed. In the current manuscript, it only describes the simple basic characteristic of this study (prospective study, COVID-19 survivors, and etc.). Second, in the results section, authors must clarify the main results of their study. Instead of describing number of patients with every single outcome (respiratory symptom, PCFS>2, fibrotic lesion, impaired PFT), it would be better if they simply describe the number of patients with main outcomes of interests (persistent symptom & fibrotic pulmonary lesion). In addition, authors must describe which factors were predictive for each outcome, before describing the AUC of their models. Third, conclusion comments do not seem to reflect the main purpose of this study. As shown in their title, I think the main purpose of this study was to build a predictive model for post-COVID lung sequelae.
Reply 2: Thank you for your suggestion. Summarizing such a large study in 250 words is challenging. We'll try to answer the questions raised by the reviewer:
Abstract/Methods: We added two sentences that describe the study more clearly.
Abstract/Results: We included the comments suggested by the reviewer.
Abstract/Conclusions: We adapted conclusions to the title of the manuscript.

Comment 3: In the introduction section, it would be better if authors describe in more detail why such predictive models for identifying high risk patients for long-term sequelae are needed.
Reply 3: Thank you for your suggestion. We added a sentence at the end of the penultimate paragraph of the Introduction (prior to the objectives).
Changes in the text 3: Page 15, 1st paragraph.

Comment 4: In the method section, I think detailed information regarding how COVID-19 was diagnosed, how COVID pneumonia was defined, how ARDS was defined (the second paragraph of method section) are not needed, because most readers are already familiar with those contents.
Reply 4: Thank you for your suggestion. We deleted these definitions and maintained the references.
Changes in the text 4: Page 16, 1st paragraph.

Comment 5: In the method and result section, it would be better if authors could make some sub-headings for more clear organization of the contents.
Reply 5: Thank you. We included the following sub-headings: "Study design", "Procedures" and the existing "Statistical analysis".
Changes in the text 5: Page 16 and 18.

Comment 6: In the result section, table 3 is difficult to understand clearly. As authors have suggested to main outcomes (persistent subjective symptoms, fibrotic sequelae with impaired lung function), I think authors should describe detailed information according to these two outcomes. For example, table 3 for persistent symptoms and table 4 for fibrotic sequelae. It is very confusing now. How many patients were classified as having persistent symptoms? 179 patients with any symptom? or 46 patients with PCFS>2? It must be more clarified.
Reply 6: We realized that some results in Table 3 may be misleading. In the Results section (line 471), it is stated that there were 179 patients considered to have dyspnea, as they met the mMRC ≥1 criterion, which characteristics are described in Table 3 (demographic characteristics). However, in the "Clinical characteristics" column, patients with dyspnea were those with mMRC ≥2. Although we included a comment, it is important to clarify this point.

We assume you are asking us to remove data about Functional Status, Radiological findings and Functional respiratory Test, as they do not provide relevant information. We removed this information as you asked. However, it is not necessary to design two tables for the little information that remains. If you do not recommend otherwise, we prefer using a single table. As it contains little information, it will be clearer for the reader.

Comment 7: In fact, AUC of prediction model is always high when we test the prediction model in the original derivation cohort. Thus, it is not surprising that the authors' model had high AUC. I think it would more informative if authors describe in more detail how the final variables were selected, instead of describing high AUC of their models.
Reply 7: We agree with the reviewer in relation to the AUC. However, we prefer maintaining this information, as this parameter is generally used in this type of studies and we think it is important that readers can compare results across studies.
With regard to information about how variables were selected, we think it is described in "Statistical Analysis", line 432. "*Based on a model containing all potential covariates, the variable with the least significant p value was removed and tested using the likelihood-ratio test until all variables left in the model (at alpha = 0.05) ....*". Anyway, if the reviewer recommends including more detailed information, we will be pleased to do it.

Comment 8: Because this study does not have a validation cohort, I think making a scoring system is not actually needed for this manuscript. Subsequent study for validating this model in other cohorts may need the score.
Reply 8: Thank you for your suggestion. We assume the reviewer refers to the score provided in Table 5. We think this information is very useful, as it can be used by physicians in the two models to assess the probability that a patient develops these sequelae. In addition, this score enabled us to estimate the capacity of this score to identify these patients. Therefore, we think this Table will help other physicians validate our prognostic models. If the reviewer agrees, we will leave the Table as it is.

Comment 9: In the discussion section, authors should discuss in more detail why predictive factors are different between two main outcomes (persistent subjective symptom vs. fibrotic sequeale on imaging).

Reply 9: Thank you for your suggestion. We included a comment about this point in Page 25 ("*We decided to build two models upon realizing that functional status and history of asthma are enough for the prognosis of persistent respiratory symptoms; in contrast, the prognosis of post-COVID-19 fibrotic pulmonary lesions requires the analysis of a wider variety of variables (factors associated with the deterioration of pulmonary function along with a history of COVID-related CCU stay").*

Reviewer C

Comment 1: It does need a native English speaker with experience in medical literature to read through and make certain changes to improve the readability "Follow-up health programs are needed to attend patients acquired 364 disability, worsening of quality of life, and overuse of healthcare resources." This sentence is an example of what I am getting at.
Reply 1: Thank you for your suggestion. We will have the manuscript revised by a professional proofreader.

Comment 2: "The study was approved by the Ethics Committee of 374 the hospital (2020/305)" – what does this mean? 2020/30/05?)
Reply 2: Thank you for your question. 2020/305 is a code that indicates the year the study was approved (2020) and the code assigned to the study by the Ethics Committee (305). We included the term "Code" for clarification purposes. We can provide the letter of approval from the Ethics Committee, would the reviewer request so (available in Spanish).

Comment 3: How did you know the opacities were novel? Were there previous CXRs of the patients? Line 387
Reply 3: Thank you. It is a good point. The term "novel" is used in the definition of pneumonia. As a previous radiological image was not available for most of the patients, we decided to remove this term. Anyway, since another reviewer recommended us to remove the definition of pneumonia, as it is already known by your readers, we removed the whole definition.

Comment 4: Line 417 – how can the authors be sure these were not present prior to COVID?
Reply 4: Thank you for your question. We will try to clarify this point. HRCT was not performed during hospitalization but in follow-up visits. Therefore, we were not certain that these lesions were already present prior to COVID. This is further clarified in the Discussion section, in the limitations, Page 25, 2nd paragraph (*"Secondly, the abnormalities observed on HRCT and lung function test cannot be completely attributed to diffuse alveolar damage secondary to infection of the lung parenchyma by SARS-COV-2 and/or subsequent ARDS"*).

Comment 5: Was the DLCO corrected for Hb?
Reply 5: Yes, it was.

Comment 6: Line 457 – orotracheal intubation/tracheostomy – Is this done in your hospital outside the ICU?

Reply 6: No, it isn't. All patients who required orotracheal intubation were transferred to the CCU. Table 1 clarifies that the 54 patients that required OTI were admitted to the CCU.

Comment 7: Table 3 description is confusing – please amend

Reply 7: Table 3 describes the patients who presented respiratory symptoms, PCFS deterioration and/or radiological of functional abnormalities at the end of follow-up (52 weeks) in relation to the total of patients and to each patient group (conventional ward vs CCU stay). In the right-hand row, differences between groups are described. Then, the variables analyzed are categorized (demographic characteristics, clinical characteristics, etc). At the request of another reviewer, we already modified this table and removed the rows "Functional Status", "Radiological findings" and "Functional respiratory test".

Comment 8: Could you provide the PCFS score system? How is this validated?

Reply 8: Please, find below a description of the PCFS score system.

0: No limitations in my everyday life.
1: Negligible limitations, (still have persistent symptoms).
2: Limitations in my everyday life, occasionally need avoid or reduce usual activities.
3: Limitations in my everyday life, and I am not able to perform all usual activities.
4: Severe limitations. I am dependent from another person due to symptoms.

This scale assesses functional limitations after venous thromboembolism and subsequently adapted to COVID-19.

References:

- Klok FA, Barco S, Siegerink B. Measuring functional limitations after venous thromboembolism: a call to action. Thromb Res 2019; 178: 59–62.
- Boon GJAM, Barco S, Bertoletti L, et al. Measuring functional limitations after venous thromboembolism: optimization of the post-VTE functional status (PVFS) scale. Thromb Res 2020; 190: 45–51.
- Klok FA, Boon GJAM, Barco S, et al. The post-COVID-19 functional status scale: a tool to measure functional status over time after COVID-19. Eur Respir J 2020;56:2001494. (REFERENCE 18 OF OUR MANUSCRIPT).

Comment 9: Line 485 – CCU stay – I presumes this higher risk of abnormal resp symptoms?

Reply 9: Thank you. You are right, CCU stay was a risk factor for the development of post-COVID-19 fibrotic pulmonary lesions.

Comment 10: Line 494 – surely having asthma (currently no curable) is the reason or confounder for persistent symptoms?

Reply 10: Thank you for your comment, but we are not sure whether the reviewer is requesting us to include a clarification. The reviewer asked us whether having asthma, as a chronic disease, may be the reason or a confounder factor. We think it may be a reason, since there are other respiratory diseases such as COPD, ILD or OSA that were not considered by the predictive model. Anyway, it may also be a confounding factor.

Comment 11: Line 504 – this needs to be more descriptive please "PCFS at the initial visit; a history of bronchial asthma; gender; FVC percentage with respect to initial visit; and CCU stay are predictive factors for the development of persistent symptoms and post-COVID-19 fibrotic pulmonary lesions."

Reply 11: Thank you for your comment. In the first paragraph of the Discussion, we summarize the most relevant results of the study. More specifically, in the sentence referred to by the reviewer, we list the variables used in the predictive models. Subsequently, in the Discussion section, a more thorough description is provided of the results obtained, which are compared with the results of other series.

Comment 12: What was initial score in this study – be good to mention it here. "In the study by Taboada et al, the percentage of patients with a PCFS ≥2 at 6 months was 24.7%, which is consistent with our results, given the timing of measurements."
Reply 12: Thank you. The study by Taboada et al does not provide this information (mean initial and final score on the PCFS scale). Anyway, we have included the scores obtained in our study in Page 22, 3rd paragraph / Page 23, 1st paragraph.

Comment 13: Line 535: "The number of patients with GGO (14.2%) and lesions of undetermined course (10.3%) in our series was slightly lower than in previous studies. GGO are associated with lung parenchyma inflammation and are considered potentially reversible, although they can be observed 12 months after COVID-19 diagnosis. Lesions of undetermined course have a poorly differentiated course profile." What % resolved or retreated in your cohort?
Reply 13: Thank you for your question. As mentioned in Page 20/1st paragraph: *"Radiological findings were not compared, as chest radiography was performed in the initial visit, whereas a HRCT was performed in the final visit"*. Radiological findings are described in Table 2, according to chest X-ray performed in the initial visit and CT scan at 52 weeks. Therefore, we cannot know the percentage of lesions that disappeared.