

August 22, 2018

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 40801-revised manuscript.docx).

Title: HRCT findings in humoral primary immunodeficiencies and correlation with pulmonary function tests

Authors: Lorenzo Cereser, Marco De Carli, Paola d'Angelo, Elisa Zanelli, Chiara Zuiani, Rossano Girometti

Name of Journal: *World Journal of Radiology*

Manuscript NO: 40801

We thank reviewers 02669684, 02673247, 00225366, 0277402, and 03501976 for their positive comments. The revised manuscript incorporated suggestions of the editor and reviewers, as follows:

1. Text format has been updated according to each of the editor's specifications. In particular, as requested: we shortened the title as "HRCT findings in humoral primary immunodeficiencies and correlation with pulmonary function tests", we added the running title, the author contributions, and the article highlights (changes have been colored in red). We also rephrase the informed consent statement and recorded the audio core tip.

2. Revision has been made according to the suggestions of the reviewers.

(1) Reviewer 02669684.

Good title. Too Long introduction, needs shortening. Needs more references in the last three years.

As suggested, we shortened the introduction.

We also added the following two recent references, and modified the bibliography accordingly:

Bang TJ, Richards JC, Olson AL, Groshong SD, Gelfand EW, Lynch DA. Pulmonary Manifestations of Common Variable Immunodeficiency. *J Thorac Imaging* 2018 Jul 31 [Epub ahead of print] [DOI: 10.1097/RTI.0000000000000350]

Tashotush B, Memarpour R, Ramirez J, Bejarano P, Mehta J. Granulomatous-lymphocytic interstitial lung disease as the first manifestation of common variable immunodeficiency. *Clin Resp J* 2018; **12**:337-43 [PMID: 27243233 DOI: 10.1111/crj.12511]

(2) Reviewer 02673247.

1. **RESULTS**, *Study population and PFTs results* "There were no statistically significant differences between the two subgroups of hPIDs in terms of prevalence of both obstructive (CVID: 44.7% vs. CVID-like: 42.9%) and restrictive (CVID: 13.1% vs. CVID-like: 0%) defects ($p > 0.05$)".

Which differences for $p > 0.05$?

As requested, we specified in the text the exact p values ($p = 0.8474$ and $p = 0.2052$ for obstructive and restrictive defects, respectively).

2. In Fig. 1, Fig.2, Fig.4 and Fig.5, no arrow indicated lesions.

As requested, we added arrows to indicate the HRCT findings in figures 1, 2, 4, and 5.

(3) Reviewer 00225366.

This work performed a retrospective study on humoral primary immunodeficiency disease using HRCT. Although the result may help the readers improving their inspection skill on finding the disease in the future, this work does not have comparisons with other imaging and test results. It is very rare to justify the humoral primary immunodeficiency disease by only using one imaging method. So, the authors should provide more information how this study can combine with other tests and imaging results in order to improve the whole outcome.

We thank the reviewer for the observation. However, we believe our study methodology and results do support the reviewer statement. Indeed, we investigated the association between two different diagnostic tools, namely HRCT (which provides morphological features) and PFTs, as currently recommended [Verma N, Grimbacher B, Hurst JR. Lung disease in primary antibody deficiency. *Lancet Respir Med.* 2015; 3: 651–60].

Of note, HRCT is the only recommended imaging method for supporting diagnosis; as a consequence, we believe that any comparison with other imaging modalities would be redundant and of limited clinical significance.

The reviewer's suggestion about stratifying our results on clinical and laboratory data is of value, but unfortunately is unfeasible because of limited population (due to the rarity of the disease). Future studies on a larger and multi-institutional cohort should address this issue. However, in our opinion, the results of such correlation might be biased by pre-selection criteria used to identify patients to be addressed to imaging.

(4) Reviewer 02577402.

1. Please check the whole article and correct all grammar mistakes.

As suggested, we corrected grammatical/spelling errors in the text, and made language polishing with the help of an English mother language colleague working in our Institute of Radiology. She was now included in the acknowledgments. All changes incorporated in the re-submitted manuscript are colored in red. Of note, changes are limited to grammar, with no substantial modification of the content compared to the original version of the manuscript. We believe that English language is now suitable for publication.

2. In the figures and tables, please give the full phrases of all the abbreviations.

We thank the reviewer for the suggestion, and modified the captions of figures and tables accordingly.

3. In Table 2, please give the significance between two groups for comparison

As requested, we add a column in the Table 2 reporting all the P-values for comparison between the two groups of patients (CVID vs. CVID-like).

(5) Reviewer 03501976.

1. *It is not clear that it was done first if the HCRT or the PFTs, how long it was between the two tests and thus establish an association, which can be interfered with by unexpected clinical situations, such as lung infection or any other type of lung disease of new appearance in time.*

Thank you for the observation. HRCT and PFTs were both performed within one month from diagnosis. Patients with unstable condition (*i.e.*, infectious respiratory disease at the time of imaging) were excluded. We therefore assume that no unexpected clinical situation have influenced our population.

2. *The authors should propose a prospective study before indicating repetition HCRT in these patients given the radiation risk.*

We agree with the reviewer. We therefore rephrase a sentence in the fifth paragraph of the discussion as follow: "Our hypothesis is extrapolated from observation of baseline examinations in our population; therefore, further studies performed with specific purpose and prospective design should confirm this statement".

3. *The independent variables in the multivariate analysis should be expressed as OR and CI of 95%.*

By definition OR cannot be calculated for the variables not included in multivariate analysis. This is why we reported the OR of the variables retained in the model only. As suggested by the reviewer, we added in the text the 95% CI for those cases, which is 2.76 to 127.52 and 1.21 to 139.97 for tree-in-bud and linear and/or irregular opacities, respectively.

Thank you again for considering our manuscript for the publication on the *World Journal of Radiology*.

Sincerely,

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September 22, 2018

Dear Editor,

Please find enclosed the edited manuscript in Word format.

Title: HRCT findings in humoral primary immunodeficiencies and correlation with pulmonary function tests

Authors: Lorenzo Cereser, Marco De Carli, Paola d'Angelo, Elisa Zanelli, Chiara Zuiani, Rossano Girometti

Name of Journal: *World Journal of Radiology*

Manuscript NO: 40801

The revised manuscript has been updated according to the editor's specifications as follows:

1. We rewrote the sentences highlighted in the cross-check report as follows:
 - a. The first sentence of results in the abstract "Patients showed common variable immunodeficiency disorders (CVID) in 38/52 cases, and CVID-like condition in 14/52 cases (11 isolated IgG subclass deficiencies + 3 selective IgA deficiencies), respectively." was rephrased (as colored in red in the text): "Thirty-eight of the 52 patients with hPIDs showed common variable immunodeficiency disorders (CVID), while the remaining 14 had CVID-like conditions (i.e., 11 had isolated IgG subclass deficiencies and 3 had selective IgA deficiencies)."
 - b. The third sentence of results in the abstract "Airway wall thickening was the most frequent finding in both groups (71%). Tree-in-bud and linear and/or irregular opacities were independent predictors ($p < 0.05$) of significant obstructive defect (OR, 18.75) and restrictive defect (OR, 13.00), respectively." was rephrased (as colored in red in the text): "Airway wall thickening was the most frequent HRCT abnormality found in both CVID and CVID-like patients (71% of cases in both groups). The presence of tree-in-bud abnormalities was an independent predictor of moderate-to-severe obstructive defects at PFTs (Odds Ratio, OR, of 18.75, $p < 0.05$), while the presence of linear and/or irregular opacities was an independent predictor of restrictive defects at PFTs (OR=13.00; $p < 0.05$)"
 - c. The sentence in material and method section "detector configuration, 64×0.625 mm; reconstructed slice thickness, 1.25 mm; reconstructed interval, 1.25 mm; gantry rotation time, 0.8 s; field of view appropriate to patient size" was rephrased: "rotation time, 0.8 s; detector configuration, 64 × 0.625 mm; reconstructed section thickness and reconstructed interval, 1.25 mm; field of view according to patient size."
 - d. The sentence in material and method section "(i.e., bronchiectasis, airway wall thickening, mucus plugging, tree-in-bud, and air trapping), and/or parenchymal-interstitial abnormalities (i.e., consolidations, ground-glass opacities, linear and/or irregular opacities, nodules, and bullae/cysts)." was rephrased: "(i.e., airway wall thickening, tree-in-bud, bronchiectasis, mucus

plugging, and air trapping), and parenchymal-interstitial abnormalities (i.e., linear and/or irregular opacities, nodules, consolidations, ground-glass opacities, and bullae/cysts).”

2. As requested, we provided a language certificate by a professional English language editing company. All changes incorporated in the re-submitted manuscript are colored in blue and green. Of note, changes are limited to syntax and grammar, with no substantial modification of the content compared to the previous version of the manuscript.
3. Concerning the informed consent statement, we uploaded the first page of the study protocol that has been approved by our referring Ethical Committee, in which we specified why the informed consent was waived.

Thank you again for considering our manuscript for the publication on the *World Journal of Radiology*.

Sincerely,

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