Peer Review File
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Reviewer A

The authors reported the method for differentiating between tuberculoma and lung cancer.

At first, the authors should carefully review the grammar and spelling mistakes in the text. Please use the abbreviations correctly.

I'm wondering several sentences in the text. For example, is it true that "Tuberculoma is the most common disease of surgically removed benign solitary pulmonary solid nodules." at line 1-2? Is it true that "the treatment of pulmonary tuberculoma is dominated by chemotherapy"? et al.

The authors reported that "Of the 105 patients with benign lesions, 57 patients with non-tuberculoma were excluded". The number of non-tuberculoma was larger than the 48 tuberculoma. (Line 147-148) It may not make much sense to differentiate tuberculoma alone from lung cancer. I think this point is a fundamental problem of this research, so please explain it in the discussion.

Please provide a numerical explanation for the abbreviations and notes for each table.

Diagnostic sensitivity, specificity, and accuracy of this examination are never good result. Do the authors think that this ROC curve study can be used in real clinical practice? If you think you can use this, how can you take advantage of this?

Comment 1: The authors should carefully review the grammar and spelling mistakes in the text. Please use the abbreviations correctly.
Reply 1: Thanks for your valuable comments. We have corrected the grammar and spelling mistakes in the text with an assisting language checker, and we reviewed the usage of abbreviations.
Changes in the text: line 2, 11, 25, 29, 36, and 39, et al.

Comment 2: Is it true that "Tuberculoma is the most common disease of surgically removed benign solitary pulmonary solid nodules." at line 1-2?
Reply 2: We have further reviewed some multicenter dissertations and found some studies that could confirm our opinion (For details, see in references 3 and 13). And in multicenter studies in China, the cases of tuberculoma is much more.
Changes in the text:

Comment 3: Is it true that "the treatment of pulmonary tuberculoma is dominated by chemotherapy" ? et al.
Reply 3: The surgical indications for pulmonary tuberculoma are definite: the pulmonary tuberculoma does not respond to chemotherapy, is indistinguishable from malignancy or leads to extensive

destruction. (For details, see in references 9)
In our opinion, that many literatures indicated that surgery combined with postoperative anti-tuberculosis treatment is effective for pulmonary tuberculoma doesn 't mean surgery combined with postoperative anti-tuberculosis treatment is the best treatment. That may because most tuberculoma is diagnosed by surgical biopsy, so one of the objectives of our study is to identify patients with tuberculoma from patients with malignancy by non-surgical approaches to further investigate the efficacy of non-surgical treatment in these patients.
Changes in the text: line 233-238

Comment 4: The authors reported that "Of the 105 patients with benign lesions, 57 patients with non-tuberculoma were excluded" . The number of non-tuberculoma was larger than the 48 tuberculoma. (Line 147-148) It may not make much sense to differentiate tuberculoma alone from lung cancer. I think this point is a fundamental problem of this research, so please explain it in the discussion.
Reply 4: The pathological findings of the 105 patients with benign lesions as follows: 48 patients with tuberculoma, 37 patients with inflammatory pseudotumor, 6 patients with round pneumonia, 4 patients with organizing pneumonia, 3 patients with pulmonary sclerosing pneumocytoma, 3 patients with hamartoma, 3 patients with fungal infection, and 1 patients with bronchogenic cyst. Tuberculoma remains a major part.
The reason why our data showed that the number of non-tuberculoma was larger than the 48 tuberculoma may be that the two groups of data with similar clinical characteristics were selected to pursue the significant difference in CT features and immunocytes, but some literature showed that patients with tuberculoma are often younger than patients with lung cancer. This issue may need further study.
Changes in the text: line 242-246

Comment 5: Please provide a numerical explanation for the abbreviations and notes for each table.
Reply 5: We have added some numerical explanations for the abbreviations and notes for each table.
Changes in the text:

Comment 6: Diagnostic sensitivity, specificity, and accuracy of this examination are never good result. Do the authors think that this ROC curve study can be used in real clinical practice? If you think you can use this, how can you take advantage of this?
Reply 6: We added the data of serum levels of tumor-related markers in patients, and the univariate analyse showed that there were no significant differences in tumor markers between two groups, confirming the CD3+T cell and CD4+T cell count as potential indicators for distinguishing pulmonary tuberculoma from early malignancy. Although diagnostic sensitivity, specificity, and accuracy of this examination do not seem good, but our results provides a new and feasible idea for identification. Our study demonstrated that noncalcified SPSNs without coarse margin, vacuole, lobation, spiculation, and pleural indentation combined with high CD3+T cell count or CD4+T cell count, need to be highly vigilant for pulmonary tuberculoma. For these patients, we propose to avoid surgery and to take long term follow-up.
And in future work, we will study on the differences in immunocytes between patients with benign nodules and patients with malignant nodules to refine which nodules are suitable for follow-up and which nodules are suitable for surgery.

Changes in the text: Table 3, line 198-200, 300-303

Reviewer B

I read the manuscript entitled "Immunocyte Count Combined with CT Features for Distinguishing Pulmonary Tuberculoma from Malignancy among Noncalcified Solitary Pulmonary Solid Nodules" with great interest and I like the idea behind the study.
However, I have several remarks and suggestions for the authors:

Language:
There are numerous language and spelling mistakes throughout the entire manuscript. It needs major language revision, either by a native speaker or a dedicated software. Here are just a few examples:
- "computed tomography (CT) imaging" instead of "computer tomography(CT) imaging"
- "Various studies" instead of "Researches"
- "recent articles [23,24] have shown" instead of "some recent articles [23,24] have showed"
- Please call lesions bigger than 3 cm in size "masses" and not "nodules"

- Please unify the number of decimal places throughout the entire document.
- Please only use the common abbreviations from the literature (e.g. pulmonary nodule, PN; part-solid-nodule, PSN; ground-glass nodule, GGN).

Comment 7: There are numerous language and spelling mistakes throughout the entire manuscript. It needs major language revision, either by a native speaker or a dedicated software.
Reply 7: Thanks for your valuable comments. We have corrected the grammar and spelling mistakes in the text with an assisting language checker, and we reviewed the usage of abbreviations.
Changes in the text: line 2, 11, 25, 29, 36, and 39, et al.

Methods:
- Please add the utilized CT reconstruction algorithm.
- Please indicate who defined the gold standard of your analysis.
- As a first step of the statistical evaluation, all parameters should be correlated and strongly correlating parameters should be excluded from further analysis.
- Please clearly describe what technique was used to define the best multivariate model (e.g. backward elimination technique).

Comment 8: Please add the utilized CT reconstruction algorithm.
Reply 8: The CT images were reconstructed by standard algorithm or medium-sharp algorithm after scanning.
Changes in the text: line 114-115

Comment 9: Please indicate who defined the gold standard of your analysis.
Reply 9: Patients who were diagnosed with pulmonary tuberculoma or malignancy by operation and had definite postoperative pathological results.
Changes in the text: line 93-95

Comment 10: As a first step of the statistical evaluation, all parameters should be correlated and strongly correlating parameters should be excluded from further analysis.
Reply 10: Spearman rank correlation analysis was used to evaluate the correlation of the parameters, and strongly correlating parameters were excluded from further analysis. And the correlation analysis was performed among all the continuous variables with a p-value less than 0.05, showing that the CD3+T lymphocyte count was positively correlated with CD4+ T lymphocyte count with the highest correlation coefficient ($r = 0.845$, $p < 0.001$), and was positively correlated with CD8+ T lymphocyte count with the highest correlation coefficient ($r = 0.834$, $p < 0.001$).
Changes in the text: line 203-207

Comment 11: Please clearly describe what technique was used to define the best multivariate model (e.g. backward elimination technique).
Reply 11: Backward elimination technique was used to define the best multivariate model.
Changes in the text: line 129

Results:
a) The following sentence does not make sense to me, please clearify (page 8, lines 157-159):
"Only 1 patient among pulmonary tuberculoma group was affected with
158 pulmonary tuberculosis twenty years ago and was cured with standard antituberculous 159 scheme, and There was no difference observed between the two groups."

Comment 12: The following sentence does not make sense to me, please clearify (page 8, lines 157-159):"Only 1 patient among pulmonary tuberculoma group was affected with 158 pulmonary tuberculosis twenty years ago and was cured with standard antituberculous 159 scheme, and There was no difference observed between the two groups."
Reply 12: We wanted to show that most patients with tuberculoma had no clear history of TB, and we reedited this sentence.
Changes in the text: line 166-168

Discussion:
a) Please do not repeat general information on the topic here, this belongs into the introduction section. Focus on putting your achieved results into context with the current literature instead.
b) You state: "Benign nodules account for a large proportion common of SPSNs, mainly of which is pulmonary tuberculoma." Is this really true? To the best of my knowledge, pulmonary harmatomas are far more common than tuberculomas.
c) The biggest limitation of this study is the probable overfitting of your model, since your ROC curves are constructed on the same data, that the predictors were derived from. Your model has to be validated on an external dataset to evaluate it's true predictive value. With your current statistical concept, your results do not allow drawing any conclusions regarding the predictive capability of the models at all. Please add this major aspect to the limitations section and rephrase your entire document and especially your conclusions accordingly. Imho, your study is a starting point for further research, in which the proposed models should be properly evaluated.
d) You elaborate extensively on rare morphological features associated with tuberculoma (such as

satellite lesion, tree-in-bud pattern, air bronchogram, and vascular convergence). Please add those features to your analysis or explain why those features were not analyzed in your study.
e) Please elaborate on why the CD8+ T-cells were not different between the two groups.

Comment 13: Please do not repeat general information on the topic here, this belongs into the introduction section. Focus on putting your achieved results into context with the current literature instead.
Reply 13: We have removed some of the content in the discussion part.
Changes in the text:

Comment 14: You state: "Benign nodules account for a large proportion common of SPSNs,mainly of which is pulmonary tuberculoma." Is this really true? To the best of my knowledge, pulmonary harmatomas are far more common than tuberculomas.
Reply 14: The pathological findings of the 105 patients with benign lesions as follows: 48 patients with tuberculoma, 37 patients with inflammatory pseudotumor, 6 patients with round pneumonia, 4 patients with organizing pneumonia, 3 patients with pulmonary sclerosing pneumocytoma, 3 patients with hamartoma, 3 patients with fungal infection, and 1 patients with bronchogenic cyst. Tuberculoma remains a major part. And in multicenter studies in China, the cases of tuberculoma is much more.
Changes in the text: line 229-238

Comment 15: The biggest limitation of this study is the probable overfitting of your model, since your ROC curves are constructed on the same data, that the predictors were derived from. Your model has to be validated on an external dataset to evaluate it's true predictive value. With yourcurrent statistical concept, your results do not allow drawing any conclusions regarding the predictive capability of the models at all. Please add this major aspect to the limitations section and rephrase your entire document and especially your conclusions accordingly. Imho, your study is a starting point for further research, in which the proposed models should be properly evaluated.
Reply 15: We have added this major aspect to the limitations section and rephrased our entire document. We are well aware that the current findings are too shallow, and the predictive capability of the models have not been fully confirmed. But from our research, we confirmed the CD3+T cell and CD4+T cell count as potential indicators for distinguishing pulmonary tuberculoma from early malignancy, which will be a starting point for our further research.
Changes in the text: line 343-347, 352-357

Comment 16: You elaborate extensively on rare morphological features associated with tuberculoma (such as satellite lesion, tree-in-bud pattern,air bronchogram, and vascular convergence). Please add those features to your analysis or explain why those features were not analyzed in your study.
Reply 16: The reasons are as follows: 1) A small sample size with numerous indicators included in this study may generate deviations; 2) The incidence of these morphological features was not high in our study data, and we focused on lymphocytes in our research. We have added this aspect to the limitations section.
Changes in the text: line 338-341

Comment 17 Please elaborate on why the CD8+ T-cells were not different between the two groups.

Reply 17: Thanks for your valuable comments. CD8+ T cell is considered as a minor role during Mycobacterium tuberculosis, but our study showed that the CD8+ T cells were not different between the two groups. This may be partly attributed to the limited sample size, and there is also a possible reason that the contribution of CD8+ T cells might be small for the diagnosis of latent tuberculosis infection. The specific mechanism is not clear. Li, et al have reported a phenomenon that CD8+ T cells in peripheral blood of pre-treated TB patients showed higher levels than healthy controls, and CD8+T cell counts decreased during anti-TB therapy. As a result, we speculated that when tuberculosis transitions from active to stationary phase, like tuberculoma, the CD8+ T cells may return to normal. Changes in the text: line 327-335

Table 1:
a) Why is the total patient count n=103 and not n=100?

Table 2:
a) Please double-check: Are you really showing the maximum diameter here or is this the median diameter of the nodules?
I would suggest revising the format of the first parameter as follows:
Median (IQR) nodule diameter, mm

Comment 18: a) Why is the total patient count n=103 and not n=100? b) Please double-check: Are you really showing the maximum diameter here or is this the median diameter of the nodules?
Reply 18: We have checked and corrected the contents in the table.