

## Peer Review File

Article information: <https://dx.doi.org/10.21037/jtd-23-1939>

### Reviewer A

In this study, the authors reported the prevalence of respiratory symptoms among patients with pulmonary nodules (PNs). Additionally, they identified factors associated with respiratory symptoms. Finally, the authors concentrated on the relationship between respiratory symptoms and psychological distress in patients with PNs. I found this work to be unique; however, I have several concerns regarding the significance, the methods, and the interpretation of results.

#### Reply:

Thank you so much for your advice. We will try our best to address all your concerns and questions.

#### Comment 1:

Comments to the authors

1) The central question in this study revolves around why the patients included visited the thoracic clinic. Unlike health checkups, individuals do not typically visit a thoracic hospital without symptoms or abnormal data. Unfortunately, the manuscript does not provide this information. Patients at thoracic clinics are more likely to exhibit symptoms compared to the general population. While the authors emphasize a significant proportion of pulmonary nodule (PN) patients displaying respiratory symptoms, this occurrence may be attributed to the mentioned reason. Consequently, the findings of this study may not be generalized.

#### Reply:

Thank you for your valuable review and suggestions about our manuscript. Indeed, motivation for hospital visit could be one of a significant selection bias in our research. After thoroughly reviewing our research, we have identified a significant variable that had been overlooked in prior analyzes: the motivation for patients undergoing CT examinations.

In China, a considerable portion of the population participates in annual health examinations, motivated by personal health concerns or corporate wellness programs. Hence, over 80% of participants in our study incidentally detected pulmonary nodules during routine health check-ups, while only 279(17.1%) participants presented to our hospital because of symptom distress. We performed a subgroup analysis on health check-ups patients and obtained results similar to those of the entire cohort. We hope these modifications can improve the generalizability of research findings to some extent.

#### Changes in the text:

We added a subgroup analysis on health check-ups cohort (Page 10, line 169-177 and Figure 3).

**Results (Page 10, line 169-177)** To understand how patient motivation for CT scans might affect symptom incidence and control sampling error, we performed a subgroup analysis on individuals with incidental pulmonary nodules detected during routine health check-ups. Of all participants, 1,354 (82.9%) undergoing chest CT as part of their health check-up, their demographic and clinical characteristics can be found in Supplementary Table 2. The distribution of their respiratory symptoms is depicted in Figure 1C. Although there was a

reduction in the incidence rates of these symptoms, their distribution pattern was consistent with that observed in the entire cohort. Univariable and multivariable logistics regression were also performed (Supplementary figure 2, Figure 3). The factors associated with symptom occurrence in this subgroup are similar to those of the entire cohort.

**Comment 2:**

2) While the authors attempted to address various factors seemingly linked to respiratory symptoms, they overlooked the significance of the location of pulmonary nodules (PNs). In my understanding, diseases in the central region are more likely to exhibit symptoms compared to those in the peripheral region. Consequently, I suggest that the location of PNs should have been considered as a potentially relevant factor. If not, please provide clarification on the plausible reason.

**Reply:**

Thank you for your constructive comments and suggestions. We totally agree that the location of pulmonary nodules (PNs) is an interesting factor might contribute to the presence of respiratory symptoms. However, as this variable is not currently recognized as a criterion for determining follow-up strategies in the majority of PN guidelines, we did not include it in our investigation.

Our study intended to explore the distribution and associated factors for symptoms in patients with PNs. The potential risk factors including the properties of PNs, environmental pollution and past medical history. We consider that our data can support the conclusion of our study to some extent, and we unable to exhaustively account for all possible risk factors in each item. Regarding the location of PNs, it is a valuable factor that can further enhance the quality of the current study, but it is not essential. We will incorporate this factor in our subsequent follow-ups and may report this result in future studies. Thank you again for your suggestion.

**Comment 3:**

3) How did the authors determine that respiratory symptoms were attributed to pulmonary nodules (PN)? For instance, patients with pre-existing conditions like COPD or asthma who also have PN may exhibit respiratory symptoms, primarily linked to their underlying diseases. Therefore, it would be prudent for the authors to consider incorporating baseline respiratory conditions, beyond just pneumonia or tuberculosis, as covariates in their analysis.

**Reply:**

Thanks for your constructive suggestion again. In fact, we have collected the past medical histories including pneumonia, tuberculosis, pulmonary fungal infections, bronchitis, asthma, bronchiectasis, and pleuritis. However, due to the low prevalence of other diseases within the study population, they were not included in our previous analysis. With your guidance, we have now merged all these past medical histories into a variable named “History of pulmonary disease” and made the corresponding modification in the analysis and text.

**Changes in the text:**

We have updated the data analysis and text associated with the history of pulmonary disease (Page 7, line 111-112; Page 10, line 166-167; Table 1; Figure 2; Figure 3).

**Comment 4:**

4) How did the authors define exposure duration to environmental risk factors as greater than 1 month? This definition seems a bit confusing, especially when considering the duration criteria for respiratory symptoms (> 8 weeks). Cough and expectoration may develop before exposure to environmental risk factors. In this case, environmental factors do not seem to be the cause of respiratory symptoms.

**Reply:**

Thank you for the careful and thoughtful evaluation of our manuscript. The definition of exposure duration and duration for respiratory symptoms aims to prevent participants from reporting incidental exposure or symptoms. In our questionnaire, we indicated that exposure to environmental risk factors should be prior to the detection of nodules, while clinical symptoms should reflect the recent situation at the time of investigation. We have made changes in the text and correct the description.

However, we must acknowledge that the constraints of the study design restrict our ability to establish a causal relationship between environmental risk factors and the onset of symptoms, thus our research can only imply an association between them.

At last, we hope that these efforts adequately addressed your insightful suggestion.

**Changes in the text:**

Please check the revised description (Page 7, line 108-114).

**Methods (Page 7, line 108-114):** For the environmental risk factors, we inquired the patients whether they had exposure (>1 month) to the environmental risk factors before the detection of PNs, which encompassed passive smoking, kitchen fume pollution and environmental dust. History of pulmonary disease included pneumonia, tuberculosis, pulmonary fungal infections, bronchitis, asthma, bronchiectasis, and pleuritis. The definition of cough and expectoration in this study referred to the presence of symptom lasting over eight weeks at the time of completing the questionnaire, excluding active respiratory tract infection.

**Reviewer B**

I had assumed that small nodules were not associated with respiratory symptoms. However, your report revealed that patients often have symptoms. The association with anxiety and depression is an interesting new perspective. I have two questions that I would like you to add.

**Reply:**

Thank you for the thoughtful evaluation of our manuscript. We will ponder your suggestions.

**Comment 1:**

(1) The Hospital Anxiety and Depression Scale (HADS) is not familiar to me and I would like to see it described.

**Reply:**

Thanks for your comment. We have added a description of the Hospital Anxiety and Depression Scale with corresponding reference in the methods section, providing a concise overview of its origins, scoring method, and clinical significance.

**Changes in the text:**

We have added a description of the Hospital Anxiety and Depression Scale (Page 7, line 118-123).

**Methods (Page 7, line 118-123)** The HADS is a self-rating scale measuring the levels of anxiety and depression, was developed by Zigmond and Snaiths in 1983<sup>16</sup>. The HADS consists of two subscales used to assess anxiety and depression and is a commonly used and reliable self-reporting tool in clinical practice. Each subscale is composed of seven 4-point Likert scale questions, with the total score ranging from 0 to 21 and a higher score indicating a higher level of anxiety or depression. For each subscale, scores between 0 and 7 are within the normal range; scores  $\geq 8$  represent a potential possibility for anxiety and depression<sup>17</sup>.

**Comment 2:**

(2) The reason for chest pain is too shortsighted to be related to anxiety or depression.

**Reply:**

We are grateful and agreed with your important comment. The psychological status including anxiety and depression is one of the many contributing factors to physical symptoms, whereas it is the primary outcome measurement in our study. Therefore, we investigated the potential relationship between physical symptoms and psychological status. We acknowledge that our study can only suggest the association between symptoms and anxiety or depression, rather than establishing causality. Our previous description seems to improperly emphasize their causal relationship, which can not be support by our data analysis.

**Changes in the text:**

We have made the appropriate changes in the discussion to avoid wrong interpretation (Page 12, line 220-228).

**Discussion (Page 12, line 220-228)** Anxiety and depression can not only reduce the quality of life but also inhibit the immunity of patients and increase the risk of malignant tumor<sup>22</sup>. Our previous study indicated that PN patients with a high level of anxiety and depression were more likely to choose aggressive treatment plan, which may lead to overtreatment<sup>18</sup>. Many studies have reported the psychological issues in patients with PNs<sup>22,23</sup>. Consistent with previous studies, the present study showed that the incidence of anxiety and depression in patients with PNs were 21.0% and 13.0%. More importantly, respiratory symptoms, especially chest pain were associated with the level of psychological burden. Hence, the appropriate management of respiratory symptoms, including therapeutic intervention and patient education, might benefit these patients by mitigating their psychological distress<sup>24-26</sup>.

**Reviewer C**

The authors described the relationship between pulmonary nodules and clinical symptoms from the retrospective analysis of a large cohort.

**Comment 1:**

This article still contains fundamental issues for publication. The most critical issue was that the readers could receive no new information from this article. The authors enhanced a conclusion as “The results of our study underlined the importance of symptoms in the management of PNs.” in the manuscript, although it does not change or affect our practice.

**Reply:**

Thank you very much for your comment. We believed that patients with pulmonary nodules are a unique population that is different from patients with early-stage lung cancer, and its prevalence has notably risen due to the widespread use of CT scans. The symptom distribution in this population may differ from that of lung cancer and have not been discussed before. The importance of this study can be summarized as follows:

1. When clinical symptoms manifest in patients with pulmonary nodules, physicians can better assess the correlation between symptoms and the nature of the nodules and environmental risk factors.
2. A considerable portion of patients with pulmonary nodules requires long-term follow-up. Symptom distribution data can provide supportive data for physicians when explaining the condition to symptomatic patients.
3. Symptom distribution can set the stage for further research, such as exploring possible connections between patients' symptoms and the nature of the nodules.

**Comment 2:**

As another issue, it was patient selection. This research is based on a single institutional cohort survey, meaning the patient has a reason to visit the hospital.

**Reply:**

Thank you for your valuable suggestion. Indeed, the reason for hospital visit could be one of a significant select bias in our research. After thoroughly reviewing our research, we have identified a significant variable that had been overlooked in prior analyses: the reason for patients undergoing CT examinations.

In China, a considerable portion of the population participates in annual health examinations, motivated by personal health concerns or corporate wellness programs. Hence, more than 80% of participants in our study incidentally detected pulmonary nodules during routine health check-ups, while only 279(17.1%) participants presented to our hospital because of symptom distress. We performed a subgroup analysis on health check-ups patients and obtained results similar to those of the entire cohort. We hope these modifications can reduce the selection bias to some extent.

**Changes in the text:**

We added a subgroup analysis on health check-ups cohort (Page 10, line 169-177 and Figure 3).

**Results (Page 10, line 169-177)** To understand how patient motivation for CT scans might affect symptom incidence and control sampling error, we performed a subgroup analysis on individuals with incidental pulmonary nodules detected during routine health check-ups. Of all participants, 1,354 (82.9%) undergoing chest CT as part of their health check-up, their demographic and clinical characteristics can be found in Supplementary Table 2. The distribution of their respiratory symptoms is depicted in Figure 1C. Although there was a reduction in the incidence rates of these symptoms, their distribution pattern was consistent with that observed in the entire cohort. Univariable and multivariable logistic regression were also performed (Supplementary figure 2, Figure 3). The factors associated with symptom occurrence in this subgroup are similar to those of the entire cohort.

**Comment 3:**

In addition, pathological diagnosis becomes an exclusion criterion, which means the case of apparent lesions that are easy to diagnose are excluded from the mother population. This selection bias brings a substantial deviation in the result, making it challenging to conclude the relationship between PN and symptoms.

**Reply:**

Thank you very much for your kindly comments on our manuscript. Our study mainly focuses on patients with ‘incidentally detected pulmonary nodules.’ For these individuals, undergoing pathological examination is actually a part of their management. After pathological examination, they are essentially categorized into the group of early-stage lung cancer or other diseases and are no longer the target population of our study, as is mentioned above.

**Comment 4:**

In the discussion, the authors mentioned that PN and clinical symptoms are generally unrelated to previous reports. I totally agree with that, but if the authors intended to declare the controversial opinion instead, well-designed (e.g., all community residents included design) and not only statistically but also clinically meaningful differences should be indicated with the data.

In summary, the point of view itself is interesting, but the authors cannot solve this issue from these datasets and analyses.

**Reply:**

Response: Thank you again for your positive and constructive comments and suggestions on our manuscript. We have enhanced the statistical method section and supplemented the potential significance of this research. Please check our reply to comment 1 and comment 2. We also addressed the limitation of our study in the section of discussion.

**Comment 4:**

“which indicated an unignorable association between the PNs and respiratory symptoms.”

The authors cannot compare the percentage with different mother populations—ref #18 written in Chinese is not the best for an international journal.

**Reply:**

Thanks for your suggestion, we have removed the inappropriate expression and replace the reference in the discussion.

**Changes in the text:**

Please kindly check Page 11, line 198-201.

**Discussion (Page 11, line 198-201)** A systematic review has indicated that the prevalence of chronic cough in China was 6.22% (95% CI 5.03–7.41%), with a lower prevalence of 4.38% (95% CI 2.74–6.02%) observed in southern China<sup>19</sup>. The discrepancy in the prevalence of respiratory symptoms among individuals with PNs and the general population suggests a potential link between respiratory symptoms and PNs.

**Reviewer D**

Thank you for this article on the highly relevant subject of pulmonary nodules.

I have following comments:

**Comment 1:**

Methods:

- You need to address why the patients in your study had a CT scan preformed? Was it as a part of screening or did the patients have symptoms that led the doctor to refer the patient to a scan. This possible bias needs to be addressed more clearly.

**Reply:**

Thank you for making this valuable suggestion. Indeed, motivation for hospital visit could be one of a significant select bias in our research. After thoroughly reviewing our research, we have identified a significant variable that had been overlooked in prior analyzes: the motivation for patients undergoing CT examinations.

In China, a considerable portion of the population participates in annual health examinations, motivated by personal health concerns or corporate wellness programs. Hence, more than 80% of participants in our study incidentally detected pulmonary nodules during routine health check-ups, while only 279(17.1%) participants presented to our hospital because of symptom distress. We performed a subgroup analysis on health check-ups patients and obtained results similar to those of the entire cohort. We hope these modifications can mitigate the selection bias to a certain extent.

**Changes in the text:**

We added a subgroup analysis on health check-ups cohort (Page 10, line 169-177 and Figure 3).

**Results (Page 10, line 169-177)** To understand how patient motivation for CT scans might affect symptom incidence and control sampling error, we performed a subgroup analysis on individuals with incidental pulmonary nodules detected during routine health check-ups. Of all participants, 1,354 (82.9%) undergoing chest CT as part of their health check-up, their demographic and clinical characteristics can be found in Supplementary Table 2. The distribution of their respiratory symptoms is depicted in Figure 1C. Although there was a reduction in the incidence rates of these symptoms, their distribution pattern was consistent with that observed in the entire cohort. Univariable and multivariable logistics regression were also performed (Supplementary figure 2, Figure 3). The factors associated with symptom occurrence in this subgroup are similar to those of the entire cohort.

**Comment 2:**

Results:

- You find that patients with nodules are more likely to have symptoms, but are also more likely to be exposed to factors we know result In pulmonary symptoms. Have you adjusted for exposure? What about pulmonary conditions such as asthma, COPD, bronchiectasis? Have you adjusted for these risk factors for pulmonary symptoms?

**Reply:**

Thank you again for your positive and constructive comments and suggestions on our manuscript. We have collected the past medical histories of participants, including pneumonia, tuberculosis, pulmonary fungal infections, bronchitis, asthma, bronchiectasis, and pleuritis. However, due to the low prevalence of other diseases within the study population, they were not included in our previous analysis. With your guidance, we have now merged all these past

medical histories into a variable named “History of pulmonary disease” and made the corresponding modification in the analysis and text.

**Changes in the text:**

We have updated the data analysis and text associated with the history of pulmonary disease (Page 7, line 111-112; Page 10, line 166-167; Table 1; Figure 2; Figure 3).

**Comment 3:**

- You conclude symptoms increase the risk of anxiety.

Can you address the fact that respiratory symptoms can be a result of anxiety. Especially because you have not evaluated the severity and duration of the symptoms.

**Reply:**

We are very grateful for your comments about the manuscript. It is absolutely true that the statistical analysis in our study fails to establish a causal relationship between symptoms and anxiety or depression, only indicating their association. Hence, we have revised the inappropriate description and added more references in the discussion to support our conjecture.

**Changes in the text:**

Please kindly check Page 12, line 220-228.

**Discussion (Page 12, line 220-228)** Anxiety and depression can not only reduce the quality of life but also inhibit the immunity of patients and increase the risk of malignant tumor<sup>23</sup>. Our previous study indicated that PN patients with a high level of anxiety and depression were more likely to choose aggressive treatment plan, which may lead to overtreatment<sup>18</sup>. Many studies have reported the psychological issues in patients with PNs<sup>23,24</sup>. Consistent with previous studies, the present study showed that the incidence of anxiety and depression in patients with PNs were 21.0% and 13.0%. More importantly, respiratory symptoms, especially chest pain were associated with the level of psychological burden. Hence, the appropriate management of respiratory symptoms, including therapeutic intervention and patient education, might benefit these patients by mitigating their psychological distress<sup>25-27</sup>.

**Comment 4:**

Discussion

- 182-183 You state that chest pain could be because of inflammation and stimulation, but why do they not experience cough and expectoration. Share your thoughts on this subject.

**Reply:**

Thanks to you for your comments. We are pleased to share our perspectives with you. First, our manuscript did not emphasize that lung inflammation is unrelated to coughing and expectoration. There may be underlying connections between lung inflammation and all these symptoms. However, this implies that our original description was unclear. We have modified the manuscript text to clarify this point. Second, we consider that lung inflammation causing chest pain without inducing coughing and expectoration is plausible, such as chronic pleurisy resulting from past lung infections. The pleurisy is more likely to cause chest pain instead of cough or expectoration.

Reference:

1. Yang H, Huang J, Gao Y, Wen Z, Peng L, Ci X. Oridonin attenuates carrageenan-induced pleurisy via activation of the KEAP-1/Nrf2 pathway and inhibition of the TXNIP/NLRP3



and NF- $\kappa$ B pathway in mice. *Inflammopharmacology*. 2020 Apr;28(2):513-523. doi: 10.1007/s10787-019-00644-y. Epub 2019 Sep 25. PMID: 31552548.

2. Ebrahimzadeh A, Pagheh AS, Mousavi T, Fathi M, Moghaddam SGM. Serosal membrane tuberculosis in Iran: A comprehensive review of evidences. *J Clin Tuberc Other Mycobact Dis*. 2023 Feb 23;31:100354. doi: 10.1016/j.jctube.2023.100354. PMID: 36874623; PMCID: PMC9982686.

**Changes in the text:**

We have modified the text in discussion to avoid misunderstanding (Page 12, line 211-213).

**Discussion (Page 12, line 211-213)** Though most of the PNs are non-invasive, PNs-relevant space-occupying and chronically inflammatory stimulation could be the reasons accounting for the associations mentioned above<sup>21,22</sup>.

**Comment 5:**

- Your population is relatively young with 75 % patients being under 60 years. Discuss how this can affect the relevance of this study seen in relation to a possible screening program for lung cancer. Most of you patients do not reach the screening criteria. Lung cancer is relatively rare in the majority of your population.

**Reply:**

Thank you for this very insightful comment. As mentioned in the reply for comment 1, the majority of our participant receive CT scans in routine health check-up but not lung cancer screening. This subgroup is primarily composed of young individuals with heightened health awareness and relatively young corporate employees. This cohort, despite having a relatively low likelihood of developing lung cancer, might experiences substantial psychological distress due to the detection of pulmonary nodules and the presence of concerning symptoms. This is one of the important motivations of our study.

**Reviewer E**

This study involves participants with nodules found incidentally and not through lung cancer screening and report on their symptoms at the time of their evaluation for the nodule .75% of incidental nodules were < 10 mm and only 2% > 20mm, in patients <60 years old (75%). A total of <20% of patients had some active and some former history of smoking, without that being further characterized in pack years or further risk factors.

**Comment 1:**

major limitations of the study:

It is not clear why imaging was pursued, to begin with, but one must assume that the imaging must have been pursued due to the presence of some acute or even chronic symptoms (and potentially previously undiagnosed or underdiagnosed respiratory conditions) in these patients which is not specified in the study. The authors can consider adding the reasoning of the "incidental image"

**Reply:**

Thank you for your constructive comments and suggestions on our manuscript. It is true that reasons for hospital visit is significant in our research design.

In China, a considerable portion of the population participates in annual health examinations, motivated by personal health concerns or corporate wellness programs. Hence, over 80% of participants in our study incidentally detected pulmonary nodules during routine health check-ups, while only 279(17.1%) participants presented to our hospital because of symptom distress. We performed a subgroup analysis on health check-ups patients and obtained results similar to those of the entire cohort. We have updated the analysis results in the manuscript and provide more details about why our participants undergo CT examinations.

**Changes in the text:**

We added a subgroup analysis on health check-ups cohort (Page 10, line 169-177 and Figure 3).

**Results (Page 10, line 169-177)** To understand how patient motivation for CT scans might affect symptom incidence and control sampling error, we performed a subgroup analysis on individuals with incidental pulmonary nodules detected during routine health check-ups. Of all participants, 1,354 (82.9%) undergoing chest CT as part of their health check-up, their demographic and clinical characteristics can be found in Supplementary Table 2. The distribution of their respiratory symptoms is depicted in Figure 1C. Although there was a reduction in the incidence rates of these symptoms, their distribution pattern was consistent with that observed in the entire cohort. Univariable and multivariable logistics regression were also performed (Supplementary figure 2, Figure 3). The factors associated with symptom occurrence in this subgroup are similar to those of the entire cohort.

**Comment 2:**

The authors mention that some patients had pneumonia and one had tuberculosis. The authors can consider adding the final respiratory diagnosis following the assessment of these patients in their thoracic clinic (most of them must be infectious, postinfectious or chronic bronchitis) and they can report the final diagnosis to those that were biopsied to determine if the reported symptoms were justified ultimately by the diagnosed condition.

**Reply:**

Thank you for making this valuable suggestion. We have collected the past medical histories of participants including pneumonia, tuberculosis, pulmonary fungal infections, bronchitis, asthma, bronchiectasis, and pleuritis. However, due to the low prevalence of other diseases within the study population, they were not included in the previous analysis. After your reminder, we have now merged all these past medical histories into a variable named “prior pulmonary diseases” and made the corresponding modification in the manuscript.

Exploring the relationship between the final diagnosis of patients and their symptoms is a highly constructive suggestion. However, the current cohort of participants is still under follow-up, and the data is insufficient to support the analysis now. We will try to follow up on this in future studies.

**Changes in the text:**

We have updated the data analysis and text associated with the history of pulmonary disease (Page 7, line 111-112; Page 10, line 166-167; Table 1; Figure 2; Figure 3).

**Comment 3:**

Conceptually, the presence of a nodule, especially in subcentimeter size, is very common and it is not a disease itself. It is a manifestation of some illness, either primarily respiratory or general infectious that would cause symptoms if no other benign entity. The above limitations have to be addressed so that It gets better or more explained why the nodules alone cause the symptoms.

**Reply:**

Thank you for your very insightful comment. We fully agree with your remark. Pulmonary nodules are not a specific disease but a common finding on CT scans. With the increasing use of CT scans, more patients are being diagnosed with pulmonary nodules incidentally. Our study does not focus on a particular disease, but on individuals with incidentally discovered pulmonary nodules. Some patients may undergo a prolonged follow-up period without knowing the nature of their nodules, potentially leading to significant psychological distress if they experience symptoms seemingly linked to the nodules. Understanding symptom distribution and associated factors in this population may provide help when doctors communicate with symptomatic patients.

To reduce the impact of respiratory diseases on our results, we have implemented corresponding exclusion criteria to screen participants and set respiratory diseases history as a variable in multivariate regression analyzes. In the revised version of manuscript, we further control the respiratory diseases history of participants as mentioned in the reply of comment 2. In addition, we also addressed the selection bias in the section of discussion (Page 13, line 237-239).

At last, thanks again for your positive and constructive comments and suggestions on our manuscript.

**Reviewer F**

In this cross-sectional study the authors analysed the prevalence and type of respiratory symptoms in patients with pulmonary nodules (PNs). The value of this study is a novel (other than the prevailing views) approach to this topic. The study is very interesting and well-written. Certainly, the hospital-based design of this study might lead to a selection bias, but it was mentioned in the limitations of the study. However, in my opinion, there are still few points that need explanation:

**Reply:** Thank you for the positive feedback and we will try our best to address the questions raised.

**Comment 1:**

Methods:

- Were PNs the only abnormalities revealed in thoracic CT? If presence of any other abnormalities in CT that might have been related to clinical symptoms (bronchiectasis, pleural fluid, pulmonary consolidations, congestion, etc.) were treated as exclusion criteria for the study?

**Reply:** Thank you for making this valuable suggestion. We have reviewed the chest CT of all the participants, and patients with obvious pulmonary lesions besides pulmonary nodules are not included in the present study. In reality, such participants are not common in our study

cohort, as the vast majority of our study samples consists of individuals undergoing routine health check-up. This significant information has been added to the manuscript. Thank you for pointing this out.

**Changes in the text:**

We have revised the exclusion criteria (Page 6-7, line 97-98).

**Methods (Page 6-7, line 97-98)** (2) obvious lesions other than PNs were found on CT scan.

**Comment 2:**

- Line 74 What kind of drugs used by patients were treated as exclusion criteria?

**Reply:**

Thank you very much for your kindly comments on our manuscript. Given the high prevalence of hypertension in China, we mainly inquired about the use of angiotensin-converting enzyme inhibitor. We have modified the text to specify the drug used as exclusion criteria.

**Changes in the text:**

We have revised the exclusion criteria (Page 7, line 98-99).

**Methods (Page 7, line 98-99)** (3) currently taking angiotensin-converting enzyme inhibitor.

**Comment 3:**

- Line 88 Why only upper airway infection were used as exclusion? How about lower airway infection?

**Reply:**

Thank you very much for your comment. We excluded patients with both lower and upper airway infection, and it listed as one of the exclusion criteria. We have corrected this error in the main text.

**Changes in the text:**

We have modified the corresponding text in methods section (Page 6-7, line 96-99; Page 7, line 112-114).

**Methods (Page 6-7, line 96-99)** (3) active pulmonary infections.

**Methods (Page 7, line 112-114)** The definition of cough and expectoration in this study referred to the presence of symptom lasting over eight weeks at the time of completing the questionnaire, excluding active respiratory tract infection.

**Comment 4:**

Results:

- An analysis of probability of PNs malignancy measured by dedicated calculators and its relationship with the presence of symptoms might be interesting.

**Reply:**

Exploring the relationship between the final diagnosis of patients and their symptoms is a highly constructive suggestion. However, the current cohort of participants is still under follow-up, and the data is insufficient to support the analysis now. We will of course try to follow up on this in future studies.

**Comment 5:**

- Line 144 What kind of correlation (or other kind of relationships) was analysed between the size of pulmonary nodules and presence of chest pain?

**Reply:**

Special thanks to you for your comments. In the manuscript, we examined the relationship between pulmonary nodule size and chest pain through univariate and multivariate logistic regression analysis. The size of pulmonary nodules showed no statistically significant correlation with chest pain symptoms, whether in the entire cohort (10 to 20mm vs. <10 mm: OR=0.9, 95%CI 0.7-1.3, P=0.735; >20mm vs. <10 mm: OR=0.8, 95%CI 0.2-2.1, P=0.675) or in the health check-up cohort (10 to 20mm vs. <10 mm: OR=0.9, 95%CI 0.6-1.4, P=0.779; >20mm vs. <10 mm: OR=1.0, 95%CI 0.2-2.9, P=0.987). The current data is insufficient to support a correlation between size of pulmonary nodules and presence of chest pain.

In conclusion, I recommend submission after minor revision of the manuscript.

**Reply:** Thank you again for your comments and suggestions on our manuscript.