Original Article

Patient-reported respiratory symptoms and relevant factors in patients with pulmonary nodules

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Background: Pulmonary nodules (PNs) are commonly considered too small to cause respiratory symptoms. However, many PN patients present with respiratory symptoms of unknown origin. This study aims to explore these symptoms and identify the associated factors.

Methods: Demographic and clinical information were retrospectively collected from 1,633 patients with incidental PNs who visited the thoracic outpatient clinic of Guangdong Provincial People's Hospital. Hospital Anxiety and Depression Scale was used to assess their anxiety and depression level. Logistic regression analyzes were employed to assess the independent risk factors for respiratory symptoms and the psychological impact on patients.

Results: Among the 1,633 patients, 37.2% reported at least one respiratory symptom. The most common symptoms in patients with PNs were cough (23.6%), followed by chest pain (14.0%), expectoration (13.8%) and hemoptysis (1.3%). Patients with large PNs (>20 mm) showed significantly higher odds of having cough [odds ratio (OR) =2.5; P=0.011] and expectoration (OR =3.6; P=0.001). Patients with multiple PNs were more susceptible to chest pain compared to those with solitary PNs (OR =1.5; P=0.007). Environmental factors such as passive smoking, kitchen fume pollution, environmental dust were the consistent risk contributors to the presence of these respiratory symptoms. Comparable findings were observed among the subgroup of individuals who undergo chest computed tomography scans as a part of their routine health check-up. Presence of respiratory symptoms, especially chest pain, was associated with increased the odds of anxiety (OR =2.2; P<0.001) and depression (OR =2.5; P<0.001) in patients.

Conclusions: Respiratory symptoms are common in PN patients, exhibiting a higher prevalence in patients with larger and multiple PNs and there is a strong association with exposure to environmental risk factors. These symptoms might exacerbate the anxiety and depression level in patients.

Keywords: Pulmonary nodules (PNs); respiratory symptoms; environmental air pollution; anxiety; depression

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Introduction

Pulmonary nodule (PN) is one of the most common incidental findings on chest computed tomography (CT) (1,2). With the popularization of high-resolution CT since the last decade, especially its extensive use as a diagnostic tool during the coronavirus disease 2019 pandemic, the detection rate of PNs has shown a dramatical increase in trend (3,4). It was reported that approximately 30% of examinees who underwent CT scanning would receive a report that described the presence of PNs (5).

Despite the high prevalence of PNs, the vast majority of nodules are inflammation-related or benign in nature, manifesting an indolent growth behavior without invasiveness (6). Imaging features are the primary basis of differentiation, while symptoms and signs usually play a little role in the clinical judgement. However, a considerable proportion of patients come to the thoracic clinic and complain about their symptoms, which are indeed the main driver of their hospital visit, while the PNs are usually incidental findings upon imaging checkup.

The mainstream view is that most of the PNs are unlikely to cause any clinical symptoms, given their relatively small size and predominantly benign nature (7). Hence, the symptomatic complaints are usually overlooked and not receiving appropriate management or explanation. These symptoms, especially those related to respiratory system, are usually regarded to be nodule-related in the eyes of patients who have limited knowledge of PNs, causing undue psychological distress (8,9). Different from other diseases, the guidelines for PNs recommend a prolonged period of follow-up instead of immediate biopsy to determine the nature of the nodules. This extended follow-up duration and the concept of "cancer suspicion" will further exacerbate the psychological burden of patients. A previous research has revealed that approximately 44% of patients with PNs experience anxiety or depression, while approximately 26% of them exhibit clinically significant distress (10). We had previously reported that the presence of symptoms would significantly exacerbate the psychological burden of PN patients. Anxious patients were more inclined to choose aggressive management, including unnecessary repeated CT examinations and even surgeries (11), which would consequently impair their quality of life and increase the economic burden (12).

As a separate patient group from other diseases, the distribution pattern of symptoms among individuals with PNs is a fundamental and significant aspect of PNs research. However, to the best of our knowledge, the consideration of clinical symptoms is currently not included in almost all guidelines and cancer risk evaluation tools for PNs (13,14). No previous study had investigated the distribution pattern of respiratory symptoms and their relevant factors in PN patients, which is of vital significance in the patient-centered communication and clinical care.

Herein, we conducted a cross-sectional study with a large sample size to investigate the distribution pattern of respiratory symptoms in PN patients and explore the relevant factors contributing to these symptoms. Furthermore, we examined the association between psychological burden and clinical symptoms. We present this article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1939/rc).

Highlight box

Key findings

- This study investigated the incidence of respiratory symptoms in pulmonary nodules (PNs) patients in a relatively large cohort. It was found that the properties of PNs and environmental factors both associated with the occurrence of symptoms, which may further exacerbate the psychological burden on patients.

What is known and what is new?

- PNs are commonly considered too small to cause respiratory symptoms.
- A considerable proportion of PNs patients experienced respiratory symptoms. The nature of the nodules was associated with the presence of respiratory symptoms.

What is the implication, and what should change now?

- The results of our study underlined the potential importance of symptoms in the management of PNs.

Methods

Participants

This is a cross-sectional study conducted in the Thoracic Clinic of Guangdong Provincial People's Hospital from January 1, 2021 to February 28, 2022. Patients with incidental PNs were invited to complete a self-administered questionnaire. The inclusion criteria included: (I) diagnosed with solitary or multiple ≤3 cm PNs using high-resolution CT scan, (II) aged 18 years and over, (III) ability to sign the informed consent and complete the questionnaire. The exclusion criteria included: (I) known pathological diagnosis

of PNs by biopsy or surgery, (II) obvious lesions other than PNs were found on CT scan, (III) active pulmonary infections, (IV) currently taking angiotensin-converting enzyme inhibitor, (V) previously diagnosed mental disorder, (VI) previous history of malignancy on any sites of the body. This study was approved by the medical ethics committee of Guangdong Provincial People's Hospital (KY-Q-2021-005-03) and conducted following the guideline of the Declaration of Helsinki (as revised in 2013). Informed consent was obtained from all participants.

Data collection

The research protocol and data collection forms were predefined by a multidisciplinary expert panel formed by surgeons, public health specialists, statisticians, and patient representatives. Demographic and clinical data were collected using a self-administered questionnaire. Data including age, gender, family history of malignancy, smoking status, reasons for undergoing chest CT, number and size of PNs, environmental risk factors, history of pulmonary disease and respiratory symptoms were collected. 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 8 weeks at the time of completing the questionnaire, excluding active respiratory tract infection. Additionally, chest pain and hemoptysis were defined as symptoms occurring more than three times and cannot explained by other diseases. Participants also underwent the evaluation of psychological burden using the validated Chinese version of Hospital Anxiety and Depression Scale (HADS) (15).

The HADS is a self-rating scale measuring the levels of anxiety and depression, was developed by Zigmond and Snaith in 1983 (16). The HADS consists of two subscales: HADS-anxiety (HADS-A) and HADS-depression (HADS-D), which were used to assess anxiety and depression respectively. 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 ≥8 represent a potential possibility for anxiety and depression (17). Web-based administration of the questionnaire was the primary approach for data collection in the current study and was powered by Wen Juan Xing (www.wjx.cn) as described in our previous study (18). Patients who cannot access to internet completed their questionnaire using available tablets, paper, or oral survey.

Statistical analysis

Demographic and clinical characteristics were described using means with standard deviation (SD) for continuous data and number (percentage) for categorical data. Categorical variables were compared using Pearson's χ^2 test. There was little missing data in this dataset as it was collected through a web-based questionnaire with specific criteria for data collection. Univariate and multivariate logistic regression analyses were used to assess the correlative factors and their respective odds ratio (OR) for respiratory symptoms. The presence of multicollinearity among the variables was evaluated using the variance inflation factor, and outliers were detected using Cook's distance. The performance of the regression model was assessed by Hosmer-Lemeshow test and likelihood ratio test. All tests were two-sided, and a P value <0.05 was considered to indicate statistical significance. All statistical analyses were performed using SPSS (IBM SPSS Statistics for Windows. Version 26.0. Armonk, NY: IBM Corp) software and R 4.2.1 (https://www.r-project.org/).

Results

Demographic and clinical characteristics

A total of 1,633 participants were involved in this study, with a mean age of 47.13±11.67 years, and 61.9% of them were females (*Table 1*). The majority of participants were never-smoker (77.5%) or former-smoker (14.8%), while the current-smoker only accounted for 7.8%. The mean diameter of nodules was 8.01±4.21 mm. Seventy-six percent of the nodules were smaller than 10 mm. Among all risk factors, the proportion of patients who exposed to passive smoke, kitchen fume pollution, environmental dust was 26.3%, 31.5%, and 9.7%, respectively. In terms of past medical history, 21.5% of the participants have a history of pulmonary disease.

Table 1 Demographic and clinical characteristics of participants (n=1,633)

Variables	n (%)
Age (years)	
<35	239 (14.6)
35–59	1,153 (70.6)
≥60	241 (14.8)
Gender	
Male	622 (38.1)
Female	1,011 (61.9)
Family history of malignancy	
Yes	752 (46.1)
No	881 (53.9)
Smoking status	
Current	127 (7.8)
Former	241 (14.8)
Never	1,265 (77.5)
Size of pulmonary nodule (mm)	
<10	1,238 (75.8)
10 to 20	362 (22.2)
>20	33 (2.0)
Number of pulmonary nodules	
Solitary	837 (51.3)
Multiple	796 (48.7)
Motivation for CT scans	
Health check-up	1,354 (82.9)
Symptom distress	279 (17.1)
Risk factor	
Passive smoking	
Yes	430 (26.3)
No	1,203 (73.7)
Kitchen fume pollution	
Yes	514 (31.5)
No	1,119 (68.5)
Environmental dust	
Yes	159 (9.7)
No	1,474 (90.3)
History of pulmonary disease	
Yes	351 (21.5)
No	1,282 (78.5)

CT, computed tomography.

Distribution of respiratory symptoms and relevant factors

The distribution of respiratory symptoms is presented in *Figure 1*. Thirty-seven percent of all the participants had at least one respiratory symptom. Among them, about one-third of the patients had two or more symptoms (*Figure 1A*). The most frequent symptoms in patients with PNs was cough (23.6%), followed by chest pain (14.0%), expectoration (13.8%) and hemoptysis (1.3%, *Figure 1B*).

We further explored the association between respiratory symptoms and potential risk factors using logistic regression analyzes. The result of univariate analysis is presented in Figure S1. Variables with a significance level of P<0.05 in univariate analysis, along with the number and size of PNs and history of pulmonary disease, were included in the multivariable model. The corresponding evaluation metrics for the regression model are shown in Table S1. Regression analysis was not performed in hemoptysis, on account of the small sample size.

Regarding the presence of symptoms, patients with PNs >20 mm had higher than twice the odds to get respiratory symptoms compared with the ones having <10 mm PNs [OR =2.5; 95% confidence interval (CI): 1.2–5.2, P=0.01, *Figure 2*]. Interestingly, the number of PNs was not associated with the chance of respiratory symptoms occurrence (OR =1.0; 95% CI: 0.8–1.3; P=0.78). Examining individual symptoms, the number of PNs was found to be associated with a higher likelihood of chest pain (OR =1.5; 95% CI: 1.1–2.0; P=0.007). Patients with nodules larger than 20 mm in size exhibited a significantly higher probability of cough (OR =2.5; 95% CI: 1.2–5.2; P=0.01) and expectoration (OR =3.6; 95% CI: 1.6–7.5; P=0.001) compared to those with <10 mm nodules. In addition, environmental risk factors and medical history of pulmonary were generally associated with the occurrence of the aforementioned symptoms.

Respiratory symptoms for patients with PNs detected during health check-up

To understand how patient's motivation for CT scans might affect symptom incidence and to control sampling error, we performed a subgroup analysis on individuals with incidental PNs 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 Table S2. The distribution of their respiratory symptoms is depicted in *Figure 1C*.

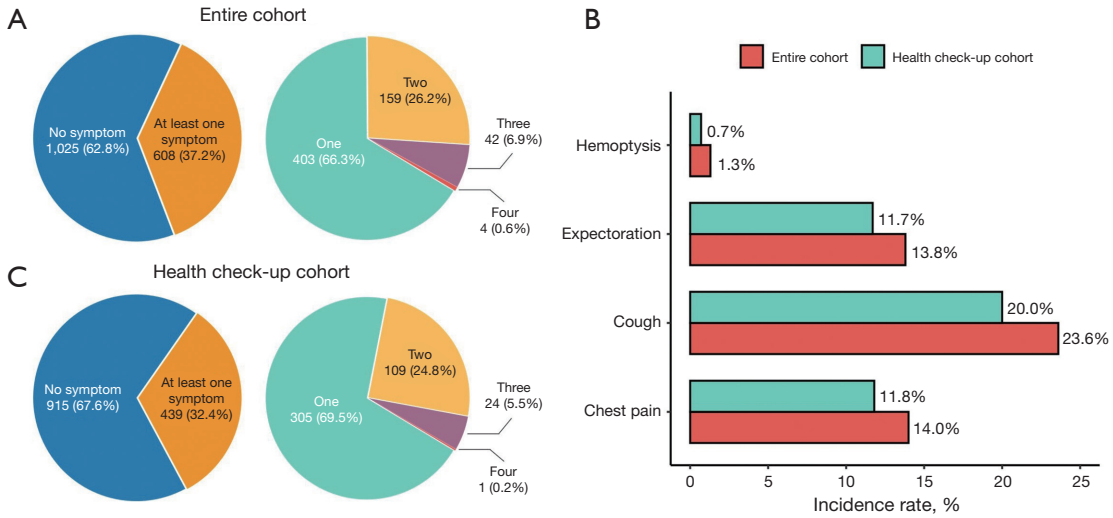

Figure 1 Distribution of respiratory symptoms among patients with pulmonary nodules. (A) Symptom prevalence and count in the entire cohort. (B) Incidence of respiratory symptoms in the entire cohort and health check-up cohort. (C) Symptom prevalence and count in the health check-up cohort.

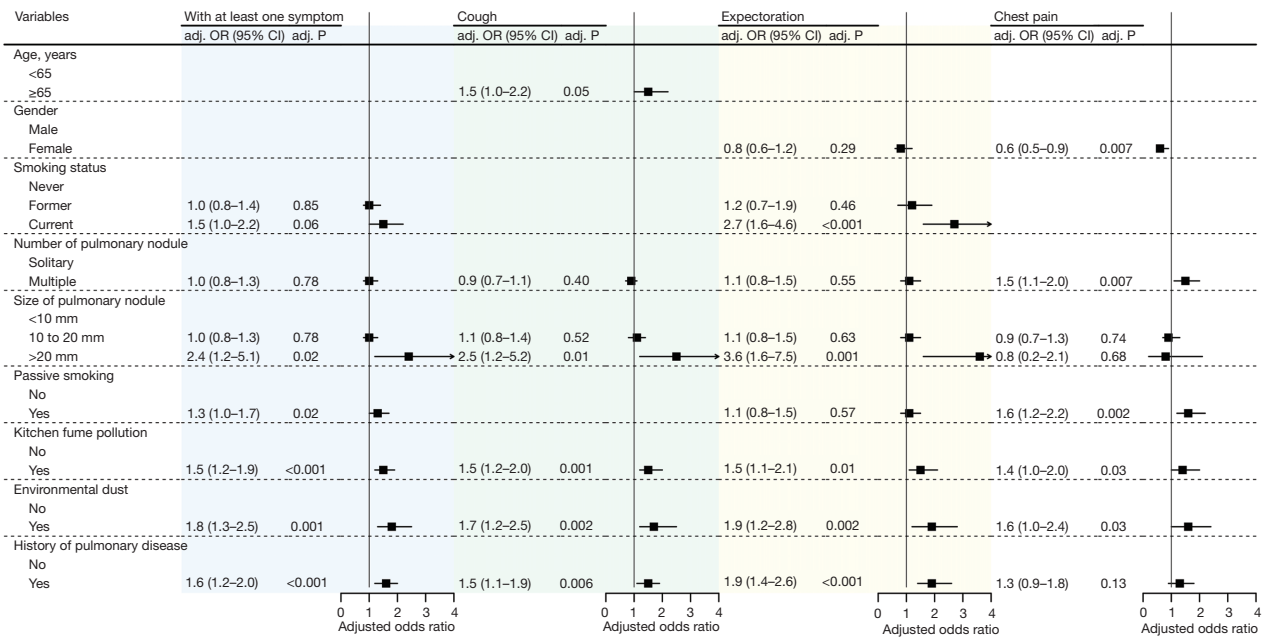

Figure 2 Multivariate logistic regression analysis for respiratory symptoms in the entire cohort. Variables with a significance level of P<0.05 in univariate analysis, along with the number and size of pulmonary nodules and past history of pulmonary disease, were considered as candidates to be included in multivariable model. adj. OR, adjusted odds ratio; CI, confidence interval; adj. P, adjusted P value.

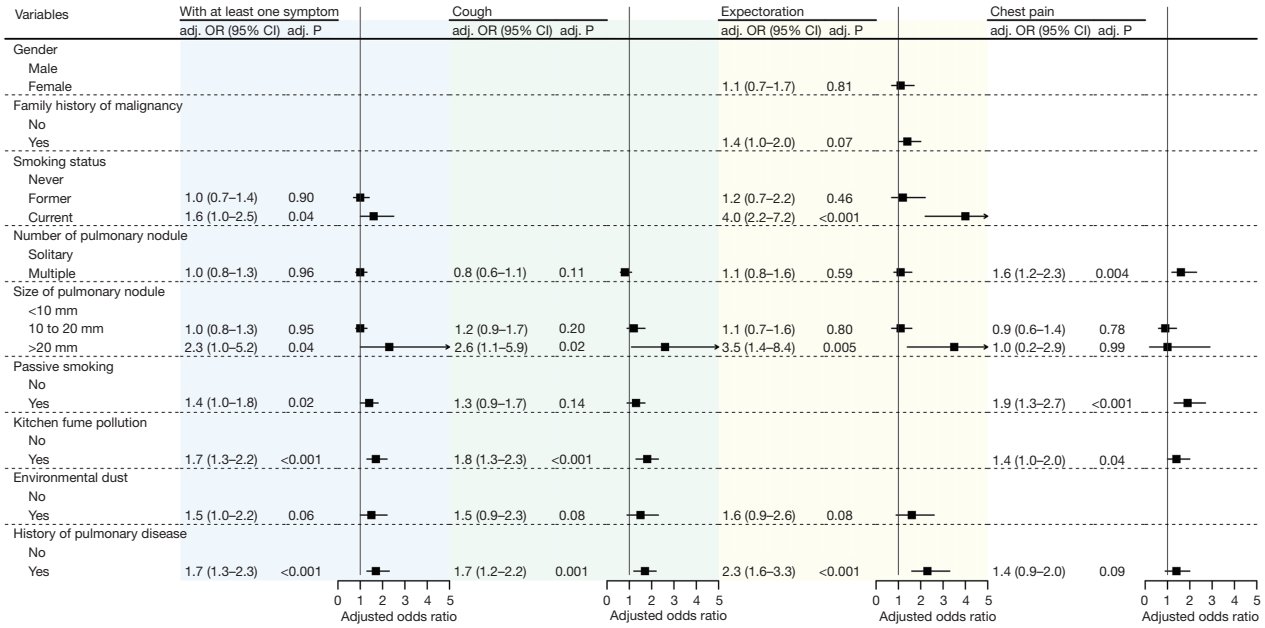

Figure 3 Multivariate logistic regression analysis for respiratory symptoms in the health check-up cohort. Variables with a significance level of P<0.05 in univariate analysis, along with the number and size of pulmonary nodules and past history of pulmonary disease, were considered as candidates to be included in multivariable model. adj. OR, adjusted odds ratio; CI, confidence interval; adj. P, adjusted P value.

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 (Figure S2, *Figure 3*). The factors associated with symptom occurrence in this subgroup are similar to those of the entire cohort.

The association between respiratory symptoms and the level of anxiety and depression

Approximately 42.7% and 26.8% of participants scored higher than 8 points on the HADS-A and HADS-D, respectively. Overall, anxiety was a more prevalent psychological burden than depression in our study population (Figure S3). To construct the multivariable model, variables with a significance level of P<0.05 in univariate analysis, along with the number and size of PNs and respiratory symptoms, were considered as candidates for inclusion (Figure S4). According to the result of adjusted multivariate regression (*Figure 4*), multiple PNs was identified as an independent risk factor for both anxiety (OR =1.5; 95% CI: 1.2–2.0; P<0.001) and depression (OR =1.7; 95% CI: 1.3–2.2; P<0.001). Additionally, chest pain was independently associated with a higher risk of anxiety (OR =2.2; 95% CI: 1.6–3.1; P<0.001) and depression (OR =2.5; 95% CI: 1.7–3.5; P<0.001) in the PN patients.

Discussion

The distribution of respiratory symptoms in patients with PNs has not been reported yet. Our study investigated the prevalence and influence factors of respiratory symptoms in patients with PNs. The results revealed that respiratory symptoms were not uncommon in patients with PNs, and the onset of respiratory symptoms was significantly associated with environmental risk factors. Particular symptoms, such as cough, expectoration or chest pain might be associated with particular factors including gender, smoking status, properties of PNs, or history of lung diseases.

Surprisingly, nearly one-third of the patients with PNs reported at least one respiratory symptom in our study. Cough, chest pain and expectoration were the three most common complaints in the participants. 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

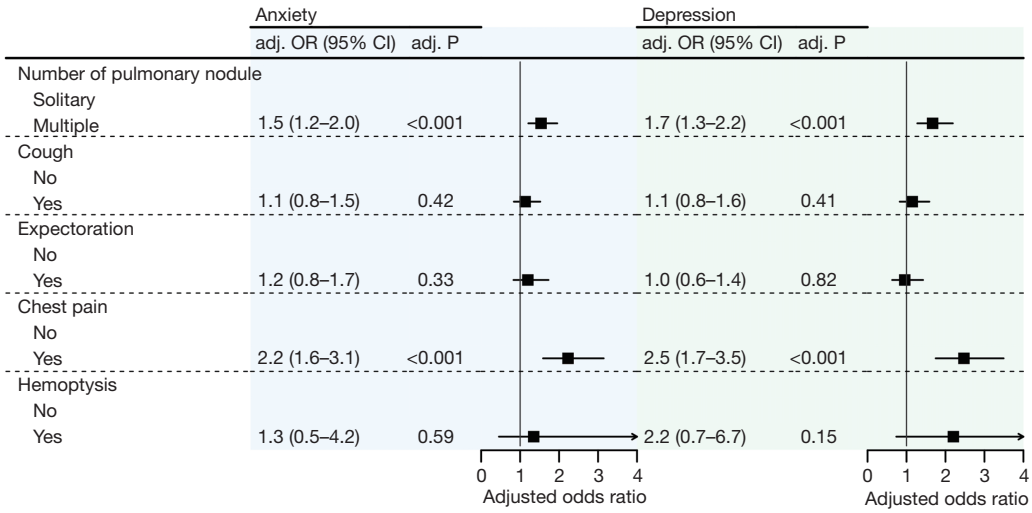

Figure 4 Multivariate logistic regression analysis of risk factors for anxiety and depression. Variables with a significance level of P<0.05 in univariate analysis, along with the number and size of pulmonary nodules and respiratory symptoms, were considered as candidates for inclusion. adj. OR, adjusted odds ratio; CI, confidence interval; adj. P, adjusted P value.

southern China (19). 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. Ruano-Raviña *et al.* reported that the most frequent symptoms in non-small cell lung cancer (NSCLC) was cough (33.0%), followed by chest pain (25.0%) and hemoptysis (11.5%), while in the stage I NSCLC these proportions were 19.1%, 10.7% and 7.0% (20). Interestingly, the prevalence rates of respiratory symptoms in the PN patients are roughly between the general population and patients with lung cancer. This ladder-like pattern highlights the potential of respiratory symptoms in the screening and malignant rate prediction of PNs. However, further studies with a larger sample size and reasonable control should be performed to validate this conjecture.

Several factors were associated the risk of respiratory symptoms in the present study. Our primary focus was on the properties of PNs themselves. PNs larger than 20 mm was an independent predictor for cough and expectoration. Multiple PNs independently increased the chance of getting chest pain. 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 (21,22). Besides the properties of PNs, smoking, environmental air pollution and the past medical history of lung diseases are also significant factors associated with the presence of respiratory symptoms. These risk factors may not only result in the formation of PNs but also cause respiratory symptoms directly. In turn, the presence of the respiratory symptoms might drive the patients to visit the hospital and lead to the increased discovery of PNs. Therefore, the relationship between risk factors, PNs and respiratory symptoms is not a causal relationship, but may be one cause with multiple effects.

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 (23). 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 (18). Many studies have reported the psychological issues in patients with PNs (23,24). 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 (25-27). To reassure anxious patients, current clinical guidelines have provided several solutions. The Fleischner Society guideline advices to shorten the follow-up period. More aggressively, some of the Chinese guidelines suggest that surgical resection might be adopted for extremely nervous patients (14,28). However, knowledge

about the indications and the benefits of aggressive management remains vague. Further research is needed to verify the impact of these suggestions.

Our study had several limitations that must be acknowledged. The cross-sectional design of the study can only reveal the correlation between significantly-associated independent and dependent variables, but cannot establish a causal relationship. Second, the severity and duration of clinical symptoms were not included in the present study, which may further elaborate the study result. Third, the hospital-based design of this study introduced the possibility of a selection bias, which may lead to an overestimation of the prevalence rate of respiratory symptoms in patients with PN (29).

Conclusions

In conclusion, the present study investigated the prevalence and distribution pattern of respiratory symptoms and its relevant factors in patients with PNs. The results indicated that a considerable proportion of PN patients were positive for respiratory symptoms. Factors including gender, environmental risk factors, properties of PNs and past medical history of pulmonary diseases may contribute to the presence of different symptoms, with environmental risk factors being the most consistent and strong signals. Finally, the presence of respiratory symptoms, especially chest pain might further exacerbate the psychological distress in patients with PNs.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1939/rc

Data Sharing Statement: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1939/dss

Peer Review File: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1939/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1939/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was approved by the medical ethics committee of Guangdong Provincial People's Hospital (KY-Q-2021-005-03) and conducted following the guideline of the Declaration of Helsinki (as revised in 2013). Informed consent was obtained from all participants.

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