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A cross-sectional study of psychological burden in Chinese patients with pulmonary nodules: Prevalence and impact on the management of nodules

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Abstract

Background: Uncertainty after the detection of pulmonary nodules (PNs) can cause psychological burden. We designed this study to quantitatively evaluate the prevalence, severity and possible impact of this burden on the preference of patients for management of nodules.

Methods: The Hospital Anxiety and Depression Scale (HADS) was used to evaluate psychological burden in patients. An independent *t*-test and a Mann–Whitney U test were used to determine the significance of differences between groups in continuous variables. A chi-square test was used to determine the significance of difference between groups in categorical variables.

Results: A total of 334 inpatients diagnosed with PNs were included in the study. A total of 17.96% of the participates screened positive for anxiety and 14.67% for depression. Female patients had significantly higher positive rates of both anxiety and depression screenings than male patients (21.57% vs. 12.31%, $p = 0.032$ and 18.05% vs. 9.30%, $p = 0.028$, respectively). Among patients screened positive for anxiety, the proportion of those who chose more aggressive management was significantly higher (34/60 vs. 113/274, $p = 0.029$). The rate of benign or precursor disease resected was significantly higher in patients with more aggressive management (46.94% vs. 9.63%, $p < 0.01$).

Conclusions: Anxiety and depression are common in Chinese patients with PNs. Patients with positive HADS anxiety screening results are more likely to adopt more aggressive management that leads to a higher rate of benign or precursor disease resected/biopsied. This study alerts clinicians to the need to assess and possibly treat emotional responses.

KEYWORDS
anxiety, depression, pulmonary nodules

INTRODUCTION

Detection of pulmonary nodules (PNs) has been reported to cause psychological burden in patients as a result of panic about lung cancer and death.[1–2] Whereas a mass detected in organs such as breast and colon have easy and instant access to biopsy and pathological diagnosis, the management of spots in the lung may cause extra cancer-related psychological burden due to "watch and wait" management. As nodules cannot be diagnosed immediately, patients have to undergo months, or even years, of surveillance in accordance with the guidelines of standard PN management before the final diagnosis, and this long wait places patients in a state of uncertainty[2–4] that is a powerful stressor and an important antecedent of anxiety.[5] Moreover, it has been reported in previous studies that because of lack of understanding of the etiology, malignancy risk and

ramification of PNs, patients' inaccurate self-diagnosis of malignancy often precedes professional evaluation of their PNs, and this may also cause considerable anxiety.[6–8] Lung cancer has been one of the deadliest cancers in China since 2008.[9–10] The survival rate of Chinese lung cancer patients in 2012–2015 was 16.8% in men and 25.1% in women, which was classified as low survival,[11] hence screening programs for the early detection of lung cancer have now become widespread in China. Yet, although there is a possibility of stage shift in lung cancer, most people screened by chest computed tomography (CT) are diagnosed with nodules that do not lead to cancer-related death.[12–13] This burden following PN detection has considerably increased lately due to the control policy of the COVID-19 pandemic: increased chest CT screenings have led to more PN detection among people of all age groups without risk factors for lung cancer.

The management of PNs remains controversial among scholars from different geographic regions and academic backgrounds, and it is revised regularly in accordance with latest studies on PNs. In general, the management recommended in Asian (including Chinese) guidelines is more aggressive than that in the US. For example, for ground-glass nodules (GGNs) no larger than 10 mm, the interval between two follow-up CT scans recommended by the Fleischner Society (FS), American College of Chest Physicians (ACCP), and National Comprehensive Cancer Network (NCCN) is 6–12 months,[3,14–15] while the interval recommended by the Chinese Alliance Against Lung Cancer and the Clinical Practice Consensus Guidelines for Asia is 3 months.[16,17]

In our department, we noticed that some patients complained of cancer-related psychological burden caused by the detection of PNs, some preferred more aggressive management due to this burden when noninvasive CT surveillance was still an appropriate choice, and some even suspended their normal living and working routines. We designed this study to quantitatively evaluate the psychological burden of Chinese PN inpatients and to explore its impact on the management of PNs in order to advocate the need to assess and possibly treat emotional responses.

METHODS

This was an observational single-center cross-sectional study conducted with the approval of the Peking University People's Hospital Medical Ethics Committee (Approval Number: 2018PHB021-01). Informed consent was obtained from the participants. The observational trial was registered at ClinicalTrials.gov (ID: NCT03498768).

Data collection

All inpatients diagnosed with PNs in the Department of Thoracic Surgery at Peking University People's Hospital from April 2018 to June 2019 were invited to complete self-administered questionnaires during inpatient education on the first day of hospitalization. Participation was voluntary and no incentives were offered. The inclusion criteria were as follows: (1) detection of noncalcified PNs with a diameter between 4–30 mm on chest CT, (2) aged between 18–80, (3) tolerant of surgery with accessible pathological diagnosis, (4) willing to receive follow-up phone calls to re-evaluate their psychological status after discharge. The exclusion criteria included: (1) difficulty in reading and writing, (2) diagnosed mental disease, (3) other circumstances deemed inappropriate for enrollment by the researchers.

At the time of enrollment, information on demographic characteristics (sex, age, education background, medical insurance, and occupational status), clinical characteristics (family history of lung cancer, history of malignant tumors, smoking history), and parameters to define more and less aggressive management (size and attenuation of the PNs, interval between two follow-up CT scans, and duration of CT surveillance until resection/biopsy) was recorded within the self-administered questionnaires.

Validated self-rating scales: Hospital anxiety and depression scale (HADS)

We used the Hospital Anxiety and Depression Scale (HADS) to evaluate patients' psychological burden. The HADS is a self-report scale that measures anxiety and depression in physically ill subjects. There are 14 items on this scale: seven for anxiety assessment and seven for depression. Each item is scored between 0 and 3.[18] The HADS scale has been translated into Chinese, validated by several Chinese groups, and recommended by the Anxiety Disorders Collaboration Group of the Chinese Medical Association Psychiatry Branch as a screening tool for Chinese inpatients since 2012.[19] The positive threshold was set at nine points for both anxiety and depression in China, and anxiety/depression with a score of over 15 is considered severe.[18,20]

Definition of more aggressive PN management

According to recommendations in the most widely-used guidelines,[3,14–17] we defined management of PNs as more aggressive any of the following criteria were met: (1) for solid nodule (SN) ≤8 mm, mixed GGN (mGGN)/pure GGN (pGGN) ≤15 mm, biopsy/resection right after the first detection of PNs; (2) an interval of less than 3 months for SN and mGGN/6 months for pGGN between two follow-up CT scans; (3) for pGGN, discontinuation of CT surveillance and biopsy/resection with no evidence of growth.

Study outcomes

The primary outcome was the prevalence and risk factors of anxiety and depression in Chinese PN patients.

The secondary outcome was the possible impact of psychological burden on the management of PNs.

Statistical analyses

First, we calculated the prevalence and severity of patients' anxiety and depression. Second, we used univariate analysis to identify which demographic or clinical variables were significant for the prediction of positive screenings of HADS in Chinese PN patients. Simple frequency, mean, standard deviation, median, and range were used to statistically describe the characteristics of participants according to type of variable. A chi-square test was used for bivariate analysis. For continuous variables, an independent *t*-test and a Mann–Whitney U test were used to determine the significance of differences between groups in continuous variables based on whether the data distribution is a parametric or nonparametric procedure, respectively.

Then we analyzed the possible impact of psychological burden on the management of PNs. All participants were grouped into patients with more or less aggressive PNs management according to the definition above. We used a Mann–Whitney U test to compare the parameters of patients in different groups. A chi-square test was then used to compare the difference in the proportion of more or less aggressive management between patients with different HADS screening outcomes. Next, we compared the rates of benign or precursor disease resected in patients with more and less aggressive management using a chi-square test.

A value of $p < 0.05$ was considered statistically significant and all *p*-values were two-tailed. All statistical procedures were conducted using IBM SPSS (v. 26.0) software for MAC.

RESULTS

A total of 451 patients completed the questionnaires. Among these, 58 patients were discharged before lung resection. Moreover, 59 patients had missing information in the questionnaires. In total, 334 patients participated in our study.

Prevalence and severity of anxiety and depression

In total, 17.96% ($n = 60$) of our participants screened positive for anxiety, 20.00% ($n = 12$) of which were severe. A total of 14.67% ($n = 49$) of the patients screened positive for depression, 12.24% ($n = 6$) of which were severe.

Positive predictor of HADS-anxiety and the HADS-depression screening

Demographic and clinical characteristics were analyzed to identify the positive predictors of anxiety screening results (Table 1). There was a significantly higher positive rate of

TABLE 1 Univariate analysis of anxiety screening results

Items		Scores of HADS anxiety subscale			Univariate analysis	
		Negative (0–8) ($n = 274$)	Positive (≥9) ($n = 60$)	Positive rate	χ^2	*p*-value[a]
Age/years (mean ± SD)		57.59 ± 10.56[b]	57.05 ± 10.31		F:0.019	0.742
Sex	Male	114	16	12.31%	4.621	0.032*
	Female	160	44	21.57%		
Family history of lung cancer	No	230	49	17.56%	0.185	0.667
	Yes	44	11	20.00%		
History of malignant tumors	No	233	46	16.49%	2.507	0.113
	Yes	41	14	25.45%		
Smoking history	No	230	54	19.01%	1.419	0.234
	Yes	44	6	12.00%		
Education background	High school and below	163	28	14.66%	3.305	0.069
	Bachelor's degree and above	111	32	22.38%		
Medical insurance	No	25	8	24.24%	0.979	0.322
	Yes	249	52	17.28%		
Occupational status	On duty	253	53	17.32%	1.027	0.311
	Retired	21	7	25.00%		

[a]Independent *t* test or the χ^2 test.
[b]Continuous variables were summarized as geometric mean ± standard deviation (SD) if normally distributed. Categorical variables were summarized as proportions.
*$p < 0.05$.

TABLE 2 Univariate analysis of depression screening results

Items		Scores of HADS depression subscale			Univariate analysis	
		Negative (0–8) ($n = 285$)	Positive (≥9) ($n = 49$)	Positive Rate	χ^2	p-value[a]
Age/years (25%–75% IQR)		59 (50–65)[b]	56 (52–64)		Z: −0.317	0.751
Sex	Male	117	12	9.30%	4.839	0.028*
	Female	168	37	18.05%		
Family history of lung cancer	No	239	40	14.34%	0.151	0.698
	Yes	46	9	16.36%		
History of malignant tumors	No	240	39	13.98%	0.648	0.421
	Yes	45	10	18.18%		
Smoking history	No	242	42	22.83%	0.021	0.884
	Yes	43	7	14.00%		
Education background	High school and below	167	24	12.57%	1.579	0.209
	Bachelor's degree and above	118	25	17.48%		
Medical insurance	No	29	4	12.12%	0.190	0.663
	Yes	256	45	14.95%		
Occupational status	On duty	264	42	13.73%	2.605	0.107
	Retired	21	7	25.00%		

[a]Mann-Whitney U test or the χ^2 test.
[b]Continuous variables were summarized as the median and 25%–75% interquartile range (IQR) if non-normally distributed. Categorical variables were summarized as proportions.
*$p < 0.05$.

TABLE 3 Characteristics of patients with more or less aggressive management

Items		PNs management		Z/χ^2	p-value[a]
		More aggressive ($n = 147$)	Less aggressive ($n = 187$)		
Time to pathological diagnosis/months		2 (0.75–5)[b]	3 (1–17.25)	−2.396	0.017*
Interval between two follow-up CT/months		1 (0.67–3)	3 (0.67–6)	−2.640	0.008*
Number of hospitals visited		3 (2–3)	3 (2–3)	−0.411	0.681
Size at surgery/mm		8 (6–11)	16 (12–22)	−11.462	<0.01*
Pathological diagnosis	Benign and precursor	46.94% (69)	9.63% (18)	59.486	<0.01*
	Malignant	53.06% (78)	90.37% (169)		

[a]Mann-Whitney U test or the χ^2 test.
[b]Continuous variables were summarized as the median and 25%–75% interquartile range (IQR) if non-normally distributed. Categorical variables were summarized as proportions.
*$p < 0.05$.

anxiety screening in female patients ($\chi^2 = 4.621$, $p = 0.032$). Patients with a higher education background were also found to be more vulnerable to anxiety ($p = 0.069$). The same data analysis process was used for the depression subscales (Table 2). The results of the univariate analysis revealed that only sex was a risk factor for positive depression screening ($\chi^2 = 4.839$, $p = 0.028$).

Comparison of patients with more or less aggressive management

According to the definition of more aggressive management, 44.01% ($n = 147$) of our patients adopted more aggressive management and 55.99% ($n = 187$) adopted less aggressive management. Our definition differentiates the two groups clearly: patients from the more aggressive group had statistically shorter durations from the detection of PNs to diagnosis (2 vs. 3 months, $p = 0.017$), shorter intervals between two follow-up CT scans (1 vs. 3 months, $p = 0.008$), and smaller diameters of PNs at the time of biopsy/resection (8 vs. 16 mm, $p < 0.01$) (Table 3).

Regarding the pathological diagnosis of PNs, 53.06% ($n = 78$) patients in the more aggressive management group had malignant nodules (including primary lung neoplasms and metastasis malignacy) and 46.94% ($n = 69$) had benign or precursor disease (including 14 adenocarcinomas in situ [AIS] and 14 atypical adenomatous hyperplasia [AAH]). In patients with less aggressive management, 90.37% ($n = 169$) had malignant nodules and 9.63% ($n = 18$) had benign or precursor disease (including 3 AIS and 2 AAH). The rate of benign or precursor disease biopsied/resected was significantly higher in

patients with more aggressive management (46.94% vs. 9.63%, $p < 0.01$) (Table 3).

Impact of anxiety and depression on the management of PNs

Among patients screened positive for anxiety, the proportion of patients with more aggressive PNs management was significantly higher than that among patients screened negative (34/60 vs. 113/274, $p = 0.029$). However, there was no statistical difference between the proportion of patients with more aggressive PN management in those screened positive or negative for depression (26/49 vs. 121/285, $p = 0.167$).

DISCUSSION

Psychological burden, including anxiety, depression, and cancer-related distress, is common in patients with screened or incidentally detected PNs worldwide. Byrne et al.[1] reported that state anxiety appeared in individuals with either indeterminate or suspicious screening results; Clark et al.[2] reported that in the Dutch–Belgian Randomized Lung Cancer Screening Trial (NELSON trial) increased cancer-specific distress appeared in those with indeterminate results. Our study revealed that anxiety and depression were also common in Chinese patients with PNs, and the positive rate of anxiety and depression screening in our PN patients was high compared with that reported in Chinese patients with other diseases.[21]

Concerning the possible risk factors of psychological burden in Chinese PN patients, our study revealed that the only positive predictor of both anxiety and depression screenings was sex. As reported by the Anxiety and Depression Association of America, the prevalence of any anxiety disorder in women was twice as high as that in men (23.4% for women and 14.3% for men), which is consistent with the results of our study.[22] In addition, Byrne et al.[1] reported that following lung cancer screenings, individuals with a higher level of education had significantly lower levels of overall state anxiety and trait anxiety than those with lower levels of education. The results of our study did not reveal any statistical difference between groups from different education backgrounds. However, patients with a higher education background were found to be more prone to anxiety (see Table 1), which contradicts the results of Byrne et al. The reason could be difference in the education system and cultural background.

Our study examines the impact of anxiety and depression on PN management. We define management of PNs as more aggressive when patients choose biopsy/resection when both noninvasive CT surveillance and invasive diagnostic process are deemed appropriate as recommended in different guidelines, as demonstrated by the three criteria given in the definition section above. First, biopsy/resection right after detection of certain PNs is usually not recommended because it has been previously reported that 10.1%–26% of PNs may decrease in size, resolve or remain stable.[23–24] The median duration from detection of PNs to biopsy/resection ranges from 11–20 months based on the size and attenuation of PNs in previous studies.[23,25] Second, our definition considered the interval between two follow-up CT scans. Recent guidelines have updated in favor of a longer CT follow-up interval ranging from 3 to 12 months depending on the size and attenuation of the PNs and the risk factors of the patients.[3,14–15] More importantly, it has been reported that a change in both solid and nonsolid PNs should be observed for at least 3 months.[23–24] Third, for subsolid nodules, biopsy/resection used to be recommended when the PNs did not resolve or decrease in the past; however, more recent guidelines have increasingly recommended that biopsy/resection should only be performed when the PNs grow, and CT surveillance should be prescribed for patients whose PNs decrease or remain stable.[23,26–27]

It is consistent with common sense that resection and CT scan "ahead-of-time" may lead to higher risk of over treatment of benign tumors, and frequent CT scans means more exposure to radiation and waste of medical resources. However, no exact number in Chinese PN patients has previously been published. In our study, the high proportion of benign or precursor disease resected/biopsied in patients with more aggressive management may provoke the controversial topic of over-diagnosis, which exists since the advocation of lung cancer screening by chest CT. In comparison, in the I-ELCAP the rate of benign disease in the surgical intervention group was 11% (54 out of 492)[28]; in the NELSON, 15% (5 out of 33) resected nodules were benign[29]; in the National Lung Screening Trial, this rate was 44%[25]; and a retrospective cohort study published on JAMA internal medicine reported that 30.8% of the participants who underwent resection had a benign nodule.[25] The rate of benign nodules resected in patients with more aggressive management in our department is actually within the range reported above. However, with the development of the healthcare system in China, chest CT screening has been introduced into routine physical examination in aged people in order to improve the prognosis of this deadliest cancer. Moreover, in accordance with the prevention of COVID-19 pandemic nowadays, the amount of CT screening increases sharply in people without risk factors for lung cancer. Without proper management of PNs, increased incidental detections may lead to more psychological burden in a larger population, as well as significant waste of medical resources. These results call for a consensus on a standardized management of PNs in the entire country, and systematic cooperation of different disciplines and medical centers for management of PN patients, which is consistent with the demand in PN management worldwide.[2,25]

In particular, the mental health of patients is not fully addressed in current PN management. The results of our study revealed that among patients screened positive for anxiety, the proportion of more aggressive PN management was significantly higher than that of those screened negative. Although the etiology of anxiety after PN detection remains unclear, it has been widely accepted that anxiety arises from

intolerance of uncertainty.[5] At PN detection, most patients were prone to overestimate cancer risk of PNs and mismatch PNs to lung cancer, and these are stressful stimuli of anxiety.[1,6–7] Instead of invasive surgery to uproot the stimuli, noninvasive methods to improve patients' tolerance of PNs could also be a choice to relieve anxiety. Koroscil et al.[8] reported that an easy-to-understand fact sheet on etiology, malignancy risk and medical consequences of PNs would improve understanding and decrease patient anxiety.

There are several limitations in our study. First, since this study was a cross-sectional study insufficient for attribution, we could only infer a possible cause-and-effect relationship between psychological burden and more aggressive PN management. The ideal design for this proposal is a prospective cohort study in a screening population in which psychological status of all patients are evaluated after detection of PNs, and then the percentages of more and less aggressive managements are compared between groups with positive and negative psychological screening outcomes. Further studies to dynamically evaluate the psychological status of PN patients are needed to determine whether surgical interventions could relieve PN patients' psychological burden, and to discover the characteristics of patients who may benefit from PNs resection psychologically. Second, this study was single-centered and only included eligible patients, which may have led to selection bias. Third, the psychological problems found in our interview were only screened but remain undiagnosed and untreated; in the biopsychosocial medical model, we should cooperate with professional psychiatrists to provide multidisciplinary care for patients with PNs.

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CONFLICT OF INTEREST

No conflict of interest to declare.

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