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Original Article

Symptom clusters and their predictors in patients with lung cancer and treated with programmed cell death protein 1 immunotherapy

Guolong Zhang [a,b], Huiwen Weng [a,c], Yinghong Li [d], Pingdong Li [e], Yucui Gong [e], Jieya Chen [e], Lin Wei [f,*], Linghui Zeng [g], Yingchun Zeng [g,*], Andy SK. Cheng [h]

[a] School of Nursing, Guangzhou University of Chinese Medicine, Guangzhou, China
[b] Guangzhou Institute of Respiratory Health, The First Affiliated Hospital of Guangzhou Medical University, Guangzhou, China
[c] Department of Oncology, The First Affiliated Hospital, Sun Yat-sen University, Guangzhou, China
[d] Department of Traditional Chinese Medicine, The First Affiliated Hospital, Sun Yat-sen University, Guangzhou, China
[e] Department of Nursing, The First Affiliated Hospital of Guangzhou Medical University, Guangzhou, China
[f] Department of Nursing, The Second Affiliated Hospital of Guangzhou University of Chinese Medicine, Guangzhou, China
[g] School of Medicine, Zhejiang University City College, Hangzhou, China
[h] Department of Rehabilitation Sciences, The Hong Kong Polytechnic University, Hong Kong SAR, China

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ABSTRACT

Objective: The aims of this study were to examine the symptom severity and interference among patients with lung cancer treated with PD-1 immunotherapy, explore whether those symptoms were clustered together, and identify factors associated with symptom clusters.

Methods: A cross-sectional study was conducted. Data were collected by demographic and clinical characteristic questionnaires and the M.D. Anderson Symptom Inventory Lung Cancer Module. Symptom clusters were identified using exploratory factor analysis, and stepwise linear regression was applied to analyze the factors affecting the symptom clusters.

Results: A total of 148 patients with lung cancer treated with PD-1 immunotherapy participated in this study. The overall symptom burdens of these patients were mainly at a mild level. The patient symptom clusters identified in this study were a general cluster, a treatment-related cluster, a pulmonary cluster, a gastrointestinal cluster, and a neural cluster. The patients' Karnofsky performance status (KPS) score ($\beta = -2.758$, $P < 0.001$) and having a history of chemotherapy ($\beta = 4.384$, $P = 0.001$) were significant predictors of the general cluster. Their KPS scores ($\beta = -1.202$, $P < 0.001$) and having a history of chemotherapy ($\beta = -1.957$, $P = 0.001$) were significant predictors of the pulmonary cluster. Their monthly income ($\beta = -0.316$, $P = 0.030$) and KPS scores ($\beta = -0.357$, $P = 0.045$) were significant predictors of the gastrointestinal cluster. Having a history of chemotherapy ($\beta = 1.868$, $P < 0.001$) was the predictor of the neural cluster.

Conclusions: The symptom burdens of patients with lung cancer and treated with PD-1 immunotherapy were at a mild level and appeared to be clustered. In addition, because the symptoms that comprise a cluster are interrelated, the diagnosis and management of each symptom in a cluster should not be performed in isolation, and each symptom in a cluster should be treated either simultaneously or in an orderly manner.

Introduction

Lung cancer is the cancer with the highest rate of diagnosis and is the leading cause of cancer-related deaths in mainland China, with nearly 2100 newly diagnosed cases of lung cancer and more than 1700 deaths from it each day in 2015.[1] Immune checkpoint inhibitors are known to be one of the most promising treatments for lung cancer, and some are even recommended as first-line treatments. Programmed cell death protein 1 (PD-1) inhibitors are some of the most common immune checkpoint inhibitors and have shown sound curative effects in patients with lung cancer.[1,2] However, lung cancer itself, as well as PD-1 immunotherapy to treat it, can result in various symptom burdens, such as physical fatigue, pain, gastrointestinal symptoms, mental disorders, sleep disturbances, and respiratory problems.[3,4] These symptom burdens can increase the

* Corresponding author.
E-mail addresses: weilin22@126.com (L. Wei), chloezengyc@hotmail.co.uk (Y. Zeng).

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patients' discomfort and shorten their overall survival.[5]

Improving symptom management during treatment is essential for patients with lung cancer. Cancer symptoms are related and they manifest as a "symptom cluster," which refers to two or more symptoms that occur concurrently and are mutually related. Unlike individual symptoms, symptom clusters seem to have a more complex and synergistic, detrimental effect on patients with cancer. Thus, clarifying the internal mechanisms of a symptom cluster should be beneficial for eliminating or alleviating the symptom severity and interferences of patients with cancer.[6]

Exploratory factor analysis (EFA) is the statistical method most used to explain the inner associations among multiple symptoms in patients with cancer. It assumes that the linear combinations of two or more symptoms create the observed variables called symptom clusters. By using the EFA analysis strategy, the internal structure or dimensions that underlie a set of observed symptoms can be revealed.

Patients with lung cancer may experience similar symptoms and symptom clusters, and the severity of their symptoms and the composition of their symptom clusters vary depending on their treatments and cancer progression. A study of Taiwanese patients with lung cancer identified a general symptom cluster and a gastrointestinal cluster that showed significant interference in the patients' daily lives.[7] Choi and Ryu[8] reported that the symptom clusters they studied were positively related to depression and showed a significant negative impact in patients with advanced lung cancer. Two other previous research studies found that many symptom clusters in patients with lung cancer receiving chemotherapy could remain stable, whereas some might change over time.[9,10] In addition, a study targeting Chinese patients with lung cancer and treated with radiotherapy reported that breathlessness, fatigue, and anxiety were involved in a symptom cluster.[11]

Notably, PD-1 immunotherapy is a novel antitumor approach that is distinct from radiotherapy and chemotherapy and that may also cause different symptom burdens and symptom clusters. As more and more symptom burdens are discovered during the use of PD-1 immunotherapy, concerns about the adverse effects and mechanisms of those symptoms are growing, and research about symptom assessment and management for patients with lung cancer with PD-1 immunotherapy is becoming increasingly urgent.

However, the composition and related factors about the symptom clusters that occur in patients with lung cancer and treated with PD-1 immunotherapy have not been reported in the past decade of its use. In addition, the incidence and severity of symptoms in patients with cancer can be affected by various factors, such as demographics and medical interventions.[12] Hence, an understanding of the inner relationships among influencing factors and symptom clusters will be beneficial toward the development of novel strategies for managing symptom severity and interferences.

The lung cancer module of the M.D. Anderson symptom inventory (MDASI-LC) is a specific scale for assessing the prevalence and severity of cancer-related or treatment-related symptoms in patients with lung cancer.[13] This instrument has been found to have good psychometric properties that reflect the symptom severity and interferences of lung cancer patients well. Thus, the objectives of this study were to describe the symptom severity and interferences of patients with lung cancer and treated with PD-1 immunotherapy, explore whether those symptoms were clustered together, and identify potential influencing factors for them, using a cross-sectional survey and the MDASI, in an effort to provide evidence for a comprehensive assessment and an individualized management strategy regarding symptoms in patients with lung cancer and treated with PD-1 immunotherapy.

Methods

Study participants

A cross-sectional design and convenience sampling method were used to enroll patients with lung cancer being treated with PD-1 immunotherapy from March 2020 to September 2021 in a general hospital at South China of Guangzhou. The inclusion criteria for patients in the study were that they (1) had a histological diagnosis of lung cancer, (2) were age $\geq$ 18 years, (3) were receiving PD-1 immunotherapy, (4) had good abilities of oral expression, word reading, listening, and writing skills, and (5) were willing to provide informed consent for participation in this study. The exclusion criteria were that a patient (1) had cognitive impairment or psychosis illness or (2) was suffering from other serious diseases.

Sample size calculation

The tool G*power 3.1 software was used to calculate the required sample size for this study. To avoid the sample size being too large or too small, we planned a medium effect size of 0.15, an alpha of 0.05, the power set at 0.8, and 15 demographic variables that were considered to be predictors, for a linear regression. A total of 139 patients were required.

Outcome measures

Demographics and clinical characteristics

We used a demographic and clinical characteristics information sheet to gather information on the participants' gender, age, marital status, area of residence, educational background, and average monthly income, and also on their clinical characteristics, such as whether the participants had a family history of lung cancer, the pathology of their disease, the duration since their initial diagnosis, whether they had a history of other types of treatments (surgery, radiation, and chemotherapy), whether their PD-1 treatment was combined with chemotherapy, what their Karnofsky performance status scale (KPS) score was, and what the specific PD-1 inhibitor in their treatment was. We chose the KPS score because it is widely used as a measure of functional status in patients with cancer, with scores ranging from 0 (death) to 100 (no symptoms nor disease). This measure has good inter-rater reliability, with a Cronbach's α coefficient greater than 0.9.[14] For this study, the patients' performance status was assessed by oncology clinicians, and the statistical data were collected by the researchers.

The lung cancer module of the M.D. Anderson Symptom Inventory

The symptom burdens of patients with lung cancer treated with PD-1 immunotherapy were measured using the lung cancer module of the M.D. Anderson Symptom Inventory.[13] The MDASI-LC consists of the severity of symptoms and daily functional impairments. The inventory's severity of symptoms section comprises 13 general symptoms (ie., fatigue, distress, appetite loss, disturbed sleep, sleepiness, sadness, shortness of breath, dry mouth, numbness, difficulty remembering, nausea, pain, and vomiting) and three disease-specific symptoms (ie., coughing, constipation, and sore throat). The daily functional impairments were relationships with others, life enjoyment, general activity, mood, work, and walking. All of the items were ranked on a 0–10 numerical scale, with a score of 0 meaning no symptoms or no impact on daily life and 10 meaning the most severe symptoms or the worst impact on daily life. There is currently no reliability and validity study of the Chinese version of MDASI-LC. On the basis of MDASI-C,[15] three lung cancer-specific items have been translated into Chinese: Sore throat to "喉咙痛", Coughing to "咳嗽", Constipation to "便秘". The Cronbach's α for the severity of 16 symptoms (13 basic symptoms and 3specific symptoms) in this study was 0.829 and for daily dysfunction was 0.929, thus suggesting an excellent internal consistency.

Data collection

Before data collection commenced, this cross-sectional survey was approved by the medical ethical committee of The First Affiliated Hospital of Guangzhou Medical University, and the final ethical approval number was IIT-2022-339. Informed consent of the participants was obtained before the survey. Data were collected by a trained oncology nurse. Data collection was conducted through face-to-face interviews, and missing data were obtained through double-checking with the patients.

Data analysis

We used the statistical software IBM SPSS Statistics version 22.0 to analyze the data in this study. Descriptive statistics were used to summarize the demographic and clinical characteristics data and the scores of the MDASI-LC. The symptom clusters were explored using principal axis factoring with the maximal rotation of variance.[16] The Kaiser-Meyer-Olkin measure (> 0.7) and Bartlett's test of sphericity ($P < 0.05$) were used to evaluate whether the data were applicable for further EFA. An eigenvalue greater than 1.0 was used to select the factors, and a factor loading greater than 0.4 was used to identify the affiliation between symptoms and their related symptom cluster. The number of factors was determined by the cumulative variance (>0.6) and a gravel diagram. Stepwise multivariate regressions were performed to explore which characteristics might be the influencing factors. The total score of each item in a symptom cluster was used as the dependent variable to enter the regression analysis model, and the covariates were selected using an entrance criterion of < 0.05 and a removal criterion of > 0.1. A step-forward approach and collinearity analysis were used in the multiple linear regression process to reduce bias due to confounding factors. A *P*-value lower than 0.05 was regarded as statistically significant in this study.

Results

Demographic and clinical characteristics of the patients

A total of 148 patients with lung cancer were included in the current study, as shown in Table 1. Most of them were males, most had been diagnosed with adenocarcinoma, and most had adopted PD-1 immunotherapy combined with chemotherapy.

Prevalence and severity of symptoms

The prevalence and severity of the symptoms in this study's lung cancer patients treated with PD-1 immunotherapy are presented in Table 2. Fatigue (79.7%, 2.71 ± 2.15), distress (82.4%, 2.53 ± 1.90), and appetite loss (77.0%, 2.49 ± 1.97) were the three symptoms with the largest percentage of severe-level ratings from respondents, but the ratings of most of the symptoms and functional impairments were in the mild range (average score < 5). The top three most prevalent daily functional impairments were relationships with others (2.90 ± 1.76), life enjoyment (2.51 ± 1.70), and general activity (2.46 ± 2.20). Details are presented in Table 3.

Symptom clusters

In this study, the value from the Kaiser-Meyer-Olkin test for sampling adequacy was 0.759, and Bartlett's test of sphericity was < 0.001, meaning that the scores of the MDASI-LC were applicable for further EFA. Five symptom clusters with eigenvalues > 1.0 were identified: a general cluster, an immunotherapy-related cluster, a pulmonary cluster, a gastrointestinal cluster, and a neural cluster, and together they could explain 68.2% of the total variance. The symptom items in each cluster were inspected. The factor analysis results are shown in Table 4.

Predictors of symptom clusters

The results of stepwise multiple linear regressions for influencing factors are presented in Table 5. The KPS score ($\beta = -2.758$, $P < 0.001$) and the combination of PD-1 with chemotherapy ($\beta = 4.384$, $P = 0.001$) were significant influencing factors of the general cluster and explained 21.9% of the total variance. Patients with a lower KPS score ($\beta = -1.202$, $P < 0.001$) and those without prior chemotherapy ($\beta = -1.957$, $P = 0.001$) tended to experience higher levels of pulmonary symptom burden, and together those factors explained 20.0% of the total variance. A low monthly income ($\beta = -0.316$, $P = 0.030$) and low KPS score ($\beta = -0.357$, $P = 0.045$) were significant predictors of gastrointestinal distress and explained 5.4% of the total variance. A history of chemotherapy ($\beta = 1.868$, $P < 0.001$) was a significant predictor of neural clusters and explained 7.8% of the total variance. None of the proposed predictors was significantly related to the immunotherapy cluster in this study.

Table 1
Demographic and clinical characteristics ($N = 148$).

Variable	*n*	%	Variable	*n*	%
Gender			Duration since diagnosis(years)		
Female	21	14.2	< 1	109	73.6
Male	127	85.8	≥ 1	39	26.4
Age (years)			History of surgery		
< 65	90	60.8	No	138	93.2
≥ 65	58	39.2	Yes	10	6.8
Marital status (Married?)			History of radiation		
No	2	1.4	No	124	83.8
Yes	146	98.6	Yes	24	16.2
Area of residence			History of chemotherapy		
Rural area	89	60.1	No	92	62.2
Downtown	37	25.0	Yes	56	37.8
City	22	14.9	PD-1 immunotherapy combined with chemotherapy		
Educational background			No	35	23.6
Primary school or below	39	26.4	Yes	113	76.4
Junior middle school	75	50.7	KPS score		
High school	17	11.5	90	80	54.1
University	7	4.7	80	43	29.1
Master's degree or above	10	6.8	70	18	12.2
Average monthly income (RMB)			60	3	2.0
0-2999	4	2.7	50	2	1.4
3000-5999	40	27.0	40	2	1.4
6000-8999	50	33.8	PD-1 inhibitors		
9000-11999	11	7.4	Camrelizumab	52	35.1
≥ 12000	43	29.1	Tislelizumab	30	20.3
Family history of lung cancer?			Sintilimab	4	2.7
No	144	97.3	Bevacizumab	8	5.4
Yes	4	2.7	Pembrolizumab	50	33.8
Pathology of disease			Nivolumab	4	2.7
Adenocarcinoma	71	48.0			
Squamous cell carcinoma	30	20.3			
Other histological types	47	31.8			

KPS, Karnofsky performance status; PD-1, programmed cell death protein 1. 1 RMB = 0.158 USD (https://www.xe.com/currencyconverter/convert/?Amount=1&From=CNY&To=USD).

Discussion

Symptom burdens of patients with lung cancer

We believe that this is the first study targeting the symptom clusters of patients with lung cancer who were treated with PD-1 immunotherapy. We found that the study participants' average scores for all aspects of symptom severity and daily functional impairment were below 3 points, which was lower than the scores reported in other studies for patients treated with chemotherapy or radiation.[7,17] That may be because treatment with immunotherapy has only a few side effects on the physical functions of patients with lung cancer.[18]

Although the overall symptom burdens of these patients were mainly at a mild level, some patients still reported moderate to severe symptoms, especially fatigue, distress, and appetite loss. Fatigue is widespread among patients with cancer and is aggravated for a period of time after chemotherapy or radiation.[19,20] Desai et al[20] also reported that fatigue (28%) was the most common adverse effect in patients with advanced solid tumors receiving intravenous tislelizumab PD-1 immunotherapy. Similar results were also found in patients with non-small-cell lung cancer and in patients with small-cell lung cancer and treated with pembrolizumab PD-1 immunotherapy.[3,21] Distress was the second most

Table 2
Mean scores for the symptoms, and the severity of symptoms, in patients with lung cancer and treated with PD-1 immunotherapy ($N = 148$).

Symptom	Mean ± SD	Without symptom, *n* (%)	Severity, *n* (%)		
			Mild (1–4)	Moderate (5–6)	Severe (7–10)
Fatigue	2.71 ± 2.15	30 (20.3)	87 (58.8)	21 (14.2)	10 (6.7)
Distress	2.53 ± 1.90	26 (17.6)	97 (65.5)	20 (13.5)	5 (3.4)
Appetite loss	2.49 ± 1.97	34 (23.0)	91 (61.5)	19 (12.8)	4 (2.7)
Disturbed sleep	1.84 ± 2.08	60 (40.5)	71 (48.0)	11 (7.4)	6 (4.1)
Drowsiness	1.69 ± 1.84	62 (41.9)	71 (48.0)	12 (8.1)	3 (2.0)
Sadness	1.60 ± 1.43	43 (29.1)	99 (66.9)	6 (4.0)	0 (0)
Shortness of breath	1.44 ± 1.63	68 (45.9)	73 (49.4)	7 (4.7)	0 (0)
Dry mouth	1.37 ± 1.72	66 (44.6)	72 (48.6)	5 (3.4)	5 (3.4)
Numbness	1.14 ± 1.85	86 (58.1)	52 (35.1)	6 (4.1)	4 (2.7)
Difficulty remembering	1.10 ± 1.54	80 (54.1)	63 (42.6)	3 (2.0)	2 (1.4)
Nausea	0.99 ± 1.59	91 (61.5)	49 (33.1)	6 (4.1)	2 (1.4)
Coughing	0.96 ± 1.45	85 (57.4)	57 (38.5)	4 (2.7)	2 (1.4)
Pain	0.87 ± 1.42	97 (65.5)	46 (31.1)	4 (2.7)	1 (0.7)
Constipation	0.52 ± 1.31	118 (79.7)	27 (18.3)	0 (0)	3 (2.0)
Vomiting	0.26 ± 0.96	132 (89.2)	14 (9.6)	0 (0)	2 (1.4)
Sore throat	0.17 ± 0.53	132 (89.2)	16 (10.8)	0 (0)	0 (0)

PD-1, programmed cell death protein 1.

Table 3
Daily functional impairment in patients with lung cancer and treated with PD-1.

Categories of impairment	Mean ± SD
Relationships with others	2.90 ± 1.76
Enjoyment of life	2.51 ± 1.70
General activity	2.46 ± 2.20
Mood	2.37 ± 1.97
Work	2.35 ± 2.26
Walking	2.11 ± 2.07

PD-1, programmed cell death protein 1.

serious symptom burden in the current study, perhaps because of the cumulative effects of the participants' cancer-related therapy, concerns about the prognosis of the disease, and medical burden.[7,10] Appetite loss was the third most serious symptom burden in this study, a finding that was similar to the findings in an earlier study by Brown.[22] This similarity may be related to the combined use of PD-1 immunotherapy and chemotherapy, which might be a significant cause of appetite loss.

Relationships with others was the most reported daily functional impairment in the current study. A possible reason for that is because the long treatment period of PD-1 immunotherapy makes it difficult for patients to keep in touch with others. In addition, the existence of cancer and the related treatments cause depression and anxiety, affect self-esteem, and eventually impact normal social activities with other people.

Finally, this study's inconsistent results compared with others' findings may be attributed to the fact that the items and scoring methods in different scales are different, and such differences will directly cause differences in the components of symptom clusters. The correlation method, factor analysis, principal component analysis, cluster analysis of symptoms and subjects, latent class analysis, and structural equation modeling are the methods commonly used to identify and model symptom clusters in oncology. Some methods use only observed variables, and some use latent variables to explain the observed phenomena. In addition, the analytic processes and mechanisms are also different, and cancer treatment varies depending on the patient's tumor type. Finally, differences in treatment can directly lead to changes in symptoms.[23]

Symptom clusters and their predictors

To the best of our knowledge, in previous studies, the symptom clusters in patients with lung cancer were manifested in multiple groups of compositions.[24] In this study, five symptom clusters were identified:

Table 4
Symptom clusters in patients with lung cancer and treated with PD-1.

Symptom clusters and their symptoms	Factor 1	Factor 2	Factor 3	Factor 4	Factor 5
General					
Fatigue	***0.878***	0.020	0.225	−0.053	0.078
Distress	***0.797***	0.247	0.240	0.152	0.098
Appetite loss	***0.773***	0.127	−0.030	0.191	−0.146
Sadness	***0.745***	0.129	0.145	0.085	0.304
Drowsiness	***0.691***	0.226	0.204	0.001	0.037
Immunotherapy-related					
Difficulty remembering	0.119	***0.790***	−0.088	0.101	−0.031
Constipation	0.253	***0.722***	−0.133	−0.065	−0.116
Sore throat	−0.034	***0.579***	0.321	−0.081	0.167
Disturbed sleep	0.347	***0.558***	0.187	0.257	0.263
Pulmonary					
Coughing	0.171	0.192	***0.720***	0.187	0.133
Dry mouth	0.359	−0.147	***0.675***	−0.100	−0.343
Shortness of breath	0.425	−0.109	***0.611***	0.001	0.210
Gastrointestinal					
Vomiting	0.063	0.096	0.008	***0.916***	0.062
Nausea	0.584	−0.171	0.210	***0.624***	−0.149
Neural					
Pain	0.050	0.132	0.170	0.076	***0.784***
Numbness	0.212	−0.356	−0.355	−0.212	***0.573***
Explained variance (%)	24.795	13.686	11.763	9.253	8.695
Cumulative variance (%)	24.795	38.482	50.245	59.498	68.193

Bold and italic values mean that these values have statistical significant, and these values were higher than 0.4, indicating these factor loadings are acceptable. PD-1, programmed cell death protein 1.

Table 5
Significant predictors for each symptom cluster, by stepwise multivariate regression.

Model of each cluster	β	S.E.	Sta. β	t	P	Adj R^2
General						
(Constant)	2.946	1.368		2.154	0.033	
KPS score	−2.758	0.571	−0.362	−4.835	<0.001	0.167
PD-1 combined with chemotherapy	4.384	1.343	0.244	3.264	0.001	0.219
Pulmonary						
(Constant)	11.711	1.470		7.966	<0.001	
KPS score	−1.202	0.270	−0.326	−4.454	<0.001	0.126
History of chemotherapy	−1.957	0.563	−0.257	−3.476	0.001	0.200
Gastrointestinal						
(Constant)	0.133	0.526		0.253	0.800	
Monthly income	−0.316	0.144	−0.174	−2.189	0.030	0.035
KPS score	−0.357	0.177	−0.161	−2.021	0.045	0.054
Neural						
(Constant)	1.678	0.255		6.580	<0.001	
History of chemotherapy	1.868	0.412	0.359	4.539	<0.001	0.078

KPS, Karnofsky performance status, the KPS score entered into the regression model as a categorical variable. PD-1, programmed cell death protein 1.

(1) the general cluster, (2) the immunotherapy-related cluster, (3) the pulmonary cluster, (4) the gastrointestinal cluster, and (5) the neural cluster. Although their compositions of symptoms have differed slightly, the core symptom clusters — the general cluster, gastrointestinal cluster, and pulmonary cluster — have tended to be consistent.[7,25] The differences in findings may result from inconsistently-used symptom assessment scales, statistical techniques, or the patients' cancer type. Notably, in our study both the gastrointestinal cluster and the neural cluster consisted of two symptoms, which would limit their variability, result in small percentage changes in a linear regression, and increase the difficulty of finding predictors. In addition, we believe that this was the first time that immunotherapy-related clusters and neurological clusters have

been identified in patients with lung cancer. Ultimately, because the clinical evidence remains lacking about symptom clusters in patients with lung cancer and treated with PD-1 immunotherapy, larger samples, and multicenter studies will still be needed in the future to verify the existence of these symptom clusters.

General symptom clusters

The general symptom cluster in this study consisted of fatigue, distress, appetite loss, sadness, and sleepiness, and that finding was most consistent with those of Wang et al.[7] Notably, we can also see that the core symptoms in this cluster match well with the clinical manifestations of fatigue, hypersomnia, and worsening of symptoms upon physical or mental exertion in systemic exertion intolerance disease. That finding may be beneficial for understanding the causes and mechanisms behind this symptom cluster. Previous studies have confirmed that systemic exertion intolerance disease is mediated by a molecular neurobiological etiology.[26] In this study, neuroanatomical and neurochemical changes were not measured directly, but from the linear regression results, we found that the KPS score and the combination of PD-1 immunotherapy with chemotherapy were significant predictors for the general cluster. Those predictive factors might also provide evidence supporting the molecular neurobiological changes represented by this symptom cluster in patients with lung cancer.

Immunotherapy-related symptom clusters

The immunotherapy-related cluster in this study consisted of four symptoms: difficulty remembering, constipation, sore throat, and disturbed sleep. Interestingly, this cluster is less similar to those reported in previous studies. Choi and Ryu[8] examined 16 symptoms and extracted a treatment-associated symptom cluster that consisted of vomiting, nausea, sleep disturbance, appetite loss, and pain in patients with advanced lung cancer. Gift et al[27] reported that sore throat, fatigue, frailty, weight loss, vomiting, appetite loss, and taste changes were identified as treatment-related symptom clusters in patients with lung cancer. As we have stated, patients with lung cancer exhibit completely different symptom clusters in conjunction with the different treatment approaches. In addition, this study found no statistically significant influencing factors related to immunotherapy-related symptom clusters. The relationship between PD-1 immunotherapy and its related symptoms and possible factors influencing the symptom cluster needs further exploration.

Pulmonary symptom clusters

Consistently with previous studies,[8–10] the pulmonary cluster in this study consisted of coughing, shortness of breath, and dry mouth. Coughing and shortness of breath are associated with a tumor in a lung-specific disease progression and/or with the treatments targeting the lung cancer.[8] Mucus drainage and oxygen inhalation will lead to fluid loss of airway, which may explain the internal relationship of these three symptoms. The patients' KPS performance score and having a history of chemotherapy were correlated with this symptom cluster. The KPS performance score is a measurement used to assess general health and tolerance to treatment of patients with cancer. The patients with lower KPS performance scores were generally in poorer health, which may be an important reason for their increased burden of pulmonary symptoms. The relationship between having a history of chemotherapy and these symptoms may be due to the therapeutic effects of chemotherapy on tumors in specific locations within the lungs, the effects of which may be beneficial longer-term in reducing the occurrence of lung symptoms.

Gastrointestinal symptom clusters

Nausea and vomiting comprised the gastrointestinal cluster in this stud, and that too was consistent with previous research findings.[7,10] In the work by Dong et al,[28] the gastrointestinal symptoms were caused mainly by adverse reactions to the chemotherapeutic drugs, and D'Addario et al[29] reported that patients who received platinum-related chemotherapy experienced relatively more severe gastrointestinal symptoms. In this study, the results of linear regression showed that monthly income and the KPS performance score were correlated with the severity of gastrointestinal symptoms. Specifically, as was also reported by Roopchand et al,[30] we found a negative relationship between a higher monthly income and nausea/vomiting distress. Indeed, patients with a relatively higher monthly income may pay more attention to their quality of life and be able to seek additional healthcare assistance to alleviate the effects of gastrointestinal symptoms. In accord with other previous research,[31] we found that a lower KPS score was associated with a significant increase in the patients' distress from nausea and vomiting. As we stated in Section 4.5, in regard to the pulmonary cluster, the lower a patient's KPS score is, the more likely the patient is to have poor physical function, which may partly explain this relationship.

Neural symptom clusters

Pain and numbness comprised the neural cluster in our study. Interestingly, as reported by Kim et al,[32] pain and numbness in patients' hands and/or feet tend to decline markedly in patients with cancer after the completion of radiotherapy. Li et al[10] also found that pain, dry mouth, numbness, and weight loss were clustered in chemotherapy patients. Nevertheless, many patients in our study had not received chemotherapy or radiotherapy, either when they were participating in this study or before, thus providing some evidence that not only chemotherapy and radiotherapy but also immunotherapy may cause this symptom cluster.

The regression analysis showed that history of chemotherapy tended to significantly increase the burden of pain and numbness. Indeed, pain and numbness are generally considered to be the major side effects of chemotherapy and are named chemotherapy-induced peripheral neuropathy.[33] The etiology of this cluster is not entirely clear, but it may be related to inflammation changes and damage to peripheral neurons caused by chemotherapy drugs.[34] Furthermore, chemotherapy is not the only cause for these symptoms — palliative radiation therapy,[35] surgery,[36] and even PD-1 immunotherapy[23,37] have also been found to be related to pain and numbness. The mechanisms leading to this symptom cluster need further exploration.

Limitations

The current study had some limitations. First, our participants were recruited from a single-center study and via convenience sampling, which limits the generalizability of the study's findings to other populations. Second, the symptom burdens and functional impairments found in this study were limited to moderate levels and below, so data on a burden of severe symptoms are still lacking. Third, the symptoms tended to change according to the illness and treatment. The results of the cross-sectional design in this study do not accurately reflect the natural changes of symptom clusters in different treatment stages. Thus, multicentered and longitudinal studies on symptom burdens of different severities are still needed to explore the mechanisms of these symptom clusters and to identify all the influencing factors in patients with lung cancer and treated with PD-1 immunotherapy. Finally, because this study included only patients with PD-1 immunotherapy and did not include patients without PD-1 immunotherapy, future research should compare the symptom experiences of patients with PD-1 immunotherapy with those without that treatment.

Implications for practice

Although this study had several limitations, its findings indicate that the symptoms in a cluster are interrelated, the diagnosis and management of each symptom in a cluster should not be performed in isolation,

and each symptom in a cluster should be treated simultaneously or in an orderly manner. The symptom management of most clusters should always begin with an early assessment of overall health and treatment tolerance, and extra attention should be paid to patients with low monthly income and those with a history either of chemotherapy or of a combination of chemotherapy and PD-1 immunotherapy.

Conclusions

This was a comprehensive cross-sectional study that focused on the symptoms and influencing factors of patients with lung cancer and treated with PD-1 immunotherapy. The results can provide reference evidence for patient symptom assessment, clinical care, and future research. In this study, the symptom burdens of patients with lung cancer and treated with PD-1 immunotherapy were at a mild level and appeared to be clustered. Full consideration of the relationships between symptoms and possible influencing factors is essential in order to effectively manage the burden of symptoms in patients with lung cancer receiving PD-1 immunotherapy.

Author contributions

GZ and HW: Study design, draft manuscript writing and revision. YL, PL, YG, and JC: Data collection. GZ: Data analysis. YZ and LW: Supervision of the entire study process. LZ, ASKC and YC made essential revisions of this manuscript. All authors have approved the final version of the manuscript.

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Declaration of competing interest

None declared.

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Ethics statement

This study was approved by the medical ethical committee of The First Affiliated Hospital of Guangzhou Medical University (Approval No. IIT-2022-339). Informed consent of the participants was obtained before the survey.

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