

The Symptoms and Influencing Factors among Lung Cancer Patients Treated with Immune Checkpoint Inhibitors

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Abstract

Objective: To investigate the symptoms of lung cancer patients treated with immune checkpoint inhibitors and analyze the influencing factors, providing a reference for symptom management. **Methods:** A survey was conducted on 191 lung cancer patients treated with immune checkpoint inhibitors using a questionnaire based on the Chinese version of the “Treatment-Related Symptoms Checklist,” the Chinese version of the Medical Coping Modes Questionnaire, the Chinese Patient Health Questionnaire Depression Scale, and the Generalized Anxiety Disorder Scale. **Results:** The total symptom score for lung cancer patients treated with immune checkpoint inhibitors was (24.35 ± 10.32) . For patients receiving combination therapies, the symptom score was (26.01 ± 9.93) , while those receiving immune checkpoint inhibitor monotherapy had a score of (16.09 ± 8.15) . Multiple linear regression results showed that body mass index, current treatment method, depression, and the “acceptance-resignation” coping style were major factors affecting symptoms in these patients. **Conclusion:** Patients with lung cancer treated with immune checkpoint inhibitors have a significant symptom burden. Those with a body mass index of 17.4 - 18.5 kg/m², receiving immune checkpoint inhibitors combined with chemotherapy, or combined with chemotherapy and targeted therapy, with high depression scores and adopting an acceptance-resignation coping style, experience more severe overall symptoms.

Keywords

Lung Cancer, Immune Checkpoint Inhibitors, Symptoms, Symptom Burden, Medical Coping Styles, Anxiety, Depression

1. Introduction

Lung cancer is one of the most common and deadliest malignant tumors, and the emergence of immune checkpoint inhibitors (ICIs) has brought new hope to its treatment [1] [2]. Clinical trials have confirmed that compared to chemotherapy, ICIs have a higher overall safety profile, fewer side effects, and are better tolerated by patients [3] [4]. However, it cannot be ignored that while ICIs enhance the body's anti-tumor effects, they can also abnormally enhance the body's normal immune response, resulting in immune tolerance imbalance and leading to immune-related adverse events (irAEs), which trigger a series of symptoms. In severe cases, these may result in treatment interruption or even patient death [1] [3] [4]. Currently, ICIs are recommended in the guidelines for the diagnosis and treatment of lung cancer as the standard first- and second-line treatment for advanced lung cancer [1] [5]. As ICIs are increasingly applied in lung cancer patients, irAEs will affect more lung cancer patients. Therefore, it is especially necessary to promptly assess symptoms occurring during ICI treatment in lung cancer patients and to manage them in a timely manner. This study will focus on patients with lung cancer treated with immune checkpoint inhibitors to understand the current status of symptom occurrence and comprehensively explore the factors influencing symptom occurrence in these patients, providing a reference for healthcare providers in developing comprehensive symptom management strategies.

2. Subjects and Methods

2.1. Study Subjects

Using a convenience sampling method, the study involved lung cancer patients receiving immune checkpoint inhibitor treatment, both inpatients and outpatients, from a tertiary cancer specialist hospital in Guangzhou from October 2020 to January 2021. Inclusion criteria: 1) Pathologically confirmed diagnosis of lung cancer; 2) Stages II, III, or IV lung cancer according to the 8th edition of the TNM staging criteria issued by the Union for International Cancer Control in 2017; 3) Aged 18 years or older; 4) Currently receiving monotherapy or combination therapy with immune checkpoint inhibitors; 5) Able to understand, read, or write in Chinese; 6) Gave informed consent to participate in this study. Exclusion criteria: 1) Patients with a past or current diagnosis of mental illness or cognitive impairment; 2) Undisclosed condition: Patients unaware of their condition; 3) Patients currently participating in clinical trials; 4) Patients with coexisting other tumors. A total of 191 patients were effectively surveyed, and their general information is shown in **Table 1**.

2.2. Research Tools

2.2.1. General Information Questionnaire

This questionnaire was designed by the researchers based on a literature review and includes sociodemographic information and disease-related data. The sociodemographic information is filled out by the patients and verified by the investi-

gator through medical records. The disease and treatment-related data are completed by the investigator by reviewing the medical records.

2.2.2. Questionnaire Based on the Modified Chinese Version of the TRSC

The questionnaire consists of two parts. The first part includes 16 core symptom items related to cancer treatment, selected from the Chinese version of the Treatment-Related Symptoms Checklist developed and localized by the Williams team [6]. The second part is an immune module, which initially added 30 possible symptoms related to immune checkpoint inhibitor (ICI) treatment based on a literature review and clinical consultations. An expert consultation method was used to evaluate and filter these symptom items. Incorporating the experts' suggestions and preliminary survey results from patients, 18 symptoms highly related to ICI treatment were selected to form the immune module for measuring symptoms and severity in lung cancer patients undergoing ICI treatment.

The content validity of the initial questionnaire was reviewed by medical and nursing experts in immunology and lung cancer treatment, and its Content Validity Index (CVI) was obtained, including the item-level CVI (I-CVI) and the scale-level CVI (S-CVI). The final questionnaire consists of 34 items in total. Scoring follows the TRSC scoring rules, using a Likert 5-point scale, where symptoms are rated from 0 (no symptoms) to 4 (very severe), and the sum of the item scores is the total score; a higher score indicates more severe symptoms. Expert evaluation showed that the I-CVI for each item of the questionnaire ranged from 0.67 to 1.00, and the S-CVI ranged from 0.83 to 1.00. In this study, the reliability coefficient (Cronbach's α) for the questionnaire was 0.80, and the I-CVI ranged from 0.67 to 1.00.

2.2.3. Chinese Version of the Medical Coping Modes Questionnaire (MCMQ)

The MCMQ, developed by Feifel H [7], is a tool suitable for measuring coping styles in patients with various diseases. It includes three dimensions: confrontation, avoidance, and acceptance-resignation, with a total of 19 items. It was translated and revised by Shen Xiaohong [8] in 2000 into 20 items, divided into three coping strategies and dimensions: confrontation, avoidance, and resignation. It uses a Likert 4-point scale, scored from 1 to 4, with higher scores indicating a greater tendency for individuals to adopt that coping style. The Cronbach's α coefficients for the dimensions are 0.69, 0.60, and 0.76, respectively. This questionnaire has been widely used in cancer patient research [8] [9]. In this study, the overall internal consistency of Cronbach's α is 0.80, with consistency for the dimensions being 0.75, 0.60, and 0.85.

2.2.4. Generalized Anxiety Disorder Scale (GAD-7)

The GAD-7, developed by Spitzer *et al.* [10] in 2006, is a 7-item scale for screening generalized anxiety and assessing symptom severity. It uses a Likert 4-point scale, where 0 represents "not at all," and 3 represents "nearly every day," with scores ranging from 0 to 21. Scores of 0 - 4 indicate no anxiety, 5 - 9 mild anxiety, 10 -

14 moderate anxiety, and 15 or above severe anxiety, with higher scores indicating more severe anxiety symptoms [11]. Domestic studies show that the GAD-7's Cronbach's α coefficient is 0.90, and the retest reliability coefficient is 0.76, indicating good reliability and validity [12]. In this study, Cronbach's α coefficient is 0.89.

2.2.5. Chinese Version of the Patient Health Questionnaire Depression Scale (PHQ-9)

The PHQ-9 is a 9-item self-report scale revised based on the Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition) (DSM-IV) for depression screening. It uses a Likert 4-point scale, where 0 represents "not at all," and 3 represents "nearly every day," with scores ranging from 0 to 27. Higher scores indicate more severe depression symptoms: 0 - 4 for no depression, 5 - 9 for the presence of depressive symptoms, 10 - 14 for significant depressive symptoms, and 15 or above for severe depression [13]. Studies show that the PHQ-9's Cronbach's α coefficient is 0.839 [14]. In this study, the Cronbach's α coefficient is 0.79.

2.3. Data Collection Method

The study design is cross-sectional. The objective is to investigate symptoms and their influencing factors in lung cancer patients receiving immune checkpoint inhibitor therapy. Based on prior experience and relevant literature review, the estimated standard deviation is 29.72. A two-tailed test is required with $\alpha = 0.05$ and a permissible error of 5. The sample size is calculated using the following formula: $n = (Z\alpha^2 * \sigma^2) / \delta^2$. The calculated sample size $N = 136$. Considering a 10% non-response rate, this study requires a minimum of 150 participants. After obtaining informed consent, questionnaires were completed and collected on-site. A total of 193 surveys were completed for this study, with 191 valid questionnaires collected, resulting in an effective recovery rate of 99.0%.

2.4. Statistical Methods

SPSS 25.0 was used for statistical description of the data. 1) Descriptive statistics were conducted on patients' physiological, psychological, and environmental data using frequency, composition ratio, mean \pm standard deviation; symptom scores were described using frequency, composition ratio, median, and interquartile range. 2) Univariate analysis: Since all data were non-normally distributed, the rank-sum test was used for metric data, and the chi-square test was used for categorical data to make statistical inferences. 3) Correlation analysis: Coping styles, anxiety, and depression were normally distributed after testing, so Pearson correlation analysis was used to explore the relationship between patients' symptoms and coping styles, anxiety, and depression. 4) Multiple linear regression analysis was employed to explore the influencing factors of patient symptoms, with the total symptom score as the dependent variable. The significance level was set at $\alpha = 0.05$, and a two-tailed test with $P < 0.05$ was considered statistically significant.

3. Results

3.1. Symptom Occurrence in Lung Cancer Patients Treated with Immune Checkpoint Inhibitors

The symptom score for lung cancer patients treated with immune checkpoint inhibitors was (24.35 ± 10.32), with the incidence of different symptoms ranging from 12.0% to 93.2%. For patients receiving a combination of ICIs and other treatment plans, the symptom score was (26.01 ± 9.93), with the incidence of different symptoms ranging from 11.3% to 92.5%. For patients receiving ICI monotherapy, the symptom score was (16.09 ± 8.15), with the incidence of different symptoms ranging from 0% to 96.9%. A total of 70 (36.6%) patients in this study reported experiencing 16 other symptoms independently, as detailed in **Table 1** and **Table 2**.

Table 1. Symptom item scores of lung cancer patients treated with immune checkpoint inhibitors (n = 191).

Symptom Items	Containing ICIs (n = 191)		ICIs Combined with Other Treatments (n = 159)		ICIs Monotherapy (n = 32)	
	Frequency/ Composition Ratio n/%	M (P25 - P75)	Frequency/ Composition Ratio n/%	M (P25 - P75)	Frequency/ Composition Ratio n/%	M (P25 - P75)
Fatigue	178 (93.2)	2.00 (1.00 - 3.00)	147 (92.5)	2.00 (1.00 - 3.00)	31 (96.9)	2.00 (1.00 - 2.00)
Poor sleep quality	145 (75.9)	1.00 (1.00 - 2.00)	145 (91.2)	2.00 (1.00 - 2.00)	20 (62.5)	1.00 (0.00 - 2.00)
Loss of appetite	129 (67.5)	1.00 (0.00 - 2.00)	115 (72.3)	2.00 (0.00 - 2.00)	14 (43.8)	0.00 (0.00 - 1.00)
Taste changes	124 (64.9)	1.00 (0.00 - 2.00)	108 (67.9)	1.00 (0.00 - 2.00)	16 (50.0)	0.50 (0.00 - 1.00)
Cough	110 (57.6)	1.00 (0.00 - 1.00)	92 (57.9)	1.00 (0.00 - 1.00)	18 (56.3)	1.00 (0.00 - 1.00)
Hair loss	107 (56.0)	1.00 (0.00 - 3.00)	102 (64.2)	1.00 (1.00 - 3.00)	5 (15.6)	0.00 (0.00 - 0.00)
Depression	99 (51.8)	1.00 (0.00 - 1.00)	83 (52.2)	1.00 (0.00 - 1.00)	16 (50.0)	0.50 (0.00 - 1.00)
Pain-head, chest, abdomen, etc.	95 (49.7)	0.00 (0.00 - 1.00)	80 (50.3)	1.00 (0.00 - 1.00)	15 (46.9)	0.00 (0.00 - 1.00)
Decreased interest in sex	94 (49.2)	0.00 (0.00 - 1.00)	82 (51.6)	1.00 (0.00 - 1.00)	12 (37.5)	0.00 (0.00 - 1.00)
Shortness of breath	83 (43.5)	0.00 (0.00 - 1.00)	72 (45.3)	0.00 (0.00 - 1.00)	11 (34.4)	0.00 (0.00 - 1.00)
Constipation	78 (40.8)	0.00 (0.00 - 0.00)	73 (45.9)	0.00 (0.00 - 1.00)	5 (15.6)	0.00 (0.00 - 0.00)
Nausea	75 (39.4)	0.00 (0.00 - 1.00)	69 (43.4)	0.00 (0.00 - 1.00)	6 (18.8)	0.00 (0.00 - 0.00)
Mouth ulcers	49 (25.1)	0.00 (0.00 - 1.00)	45 (28.3)	0.00 (0.00 - 1.00)	4 (12.5)	0.00 (0.00 - 0.00)
Vomiting	37 (19.4)	0.00 (0.00 - 0.00)	37 (23.3)	0.00 (0.00 - 0.00)	-	-
Weight loss	30 (15.7)	0.00 (0.00 - 0.00)	27 (17.0)	0.00 (0.00 - 0.00)	3 (9.4)	1.00 (0.00 - 1.00)
Fever immune module	23 (12.0)	0.00 (0.00 - 0.00)	19 (11.9)	0.00 (0.00 - 0.00)	4 (12.5)	0.00 (0.00 - 0.00)
Decreased mental state	171 (89.5)	1.00 (1.00 - 2.00)	145 (91.2)	1.00 (0.00 - 1.00)	26 (81.3)	1.00 (1.00 - 2.00)
Urinary abnormalities	133 (69.6)	1.00 (0.00 - 2.00)	114 (71.7)	1.00 (0.00 - 2.00)	19 (59.4)	0.00 (0.00 - 1.00)
Dry mouth	122 (63.9)	1.00 (0.00 - 2.00)	99 (62.3)	1.00 (0.00 - 2.00)	23 (71.9)	1.00 (0.00 - 1.75)
Itching	103 (53.9)	1.00 (0.00 - 2.00)	85 (53.5)	0.00 (0.00 - 1.00)	18 (56.3)	1.00 (0.00 - 1.75)
Bloating sensation	94 (49.2)	0.00 (0.00 - 2.00)	88 (55.3)	1.00 (0.00 - 2.00)	6 (18.8)	0.00 (0.00 - 0.00)
Muscle soreness	91 (47.6)	0.00 (0.00 - 2.00)	61 (38.4)	1.00 (0.00 - 2.00)	9 (28.1)	0.00 (0.00 - 1.00)

Continued

Chills	91 (47.6)	0.00 (0.00 - 1.00)	77 (48.4)	0.00 (0.00 - 1.00)	14 (43.8)	0.00 (0.00 - 1.00)
Peripheral sensory abnormalities	86 (45.0)	0.00 (0.00 - 2.00)	78 (49.1)	0.00 (0.00 - 2.00)	8 (25.0)	0.00 (0.00 - 0.75)
Joint pain	79 (41.4)	0.00 (0.00 - 1.00)	71 (44.7)	0.00 (0.00 - 1.00)	8 (25.0)	0.00 (0.00 - 0.75)
Skin changes	72 (37.7)	0.00 (0.00 - 2.00)	59 (57.1)	0.00 (0.00 - 2.00)	13 (40.6)	0.00 (0.00 - 1.75)
Increased sweating	63 (33.0)	0.00 (0.00 - 1.00)	61 (38.4)	0.00 (0.00 - 1.00)	2 (6.3)	0.00 (0.00 - 0.00)
Blurred vision	61 (31.9)	0.00 (0.00 - 1.00)	53 (33.3)	0.00 (0.00 - 1.00)	8 (25.0)	0.00 (0.00 - 0.75)
Weight gain	56 (29.3)	0.00 (0.00 - 1.00)	46 (28.9)	0.00 (0.00 - 1.00)	10 (31.3)	0.00 (0.00 - 0.00)
Palpitations, rapid heartbeat	55 (28.8)	0.00 (0.00 - 1.00)	50 (31.4)	0.00 (0.00 - 1.00)	5 (15.6)	0.00 (0.00 - 0.00)
Dizziness	55 (28.8)	0.00 (0.00 - 1.00)	48 (30.2)	0.00 (0.00 - 1.00)	7 (21.9)	0.00 (0.00 - 0.00)
Difficulty breathing	44 (23.0)	0.00 (0.00 - 0.00)	43 (27.0)	0.00 (0.00 - 1.00)	1 (3.1)	0.00 (0.00 - 0.00)
Photophobia	28 (14.7)	0.00 (0.00 - 0.00)	26 (16.4)	0.00 (0.00 - 0.00)	2 (6.3)	0.00 (0.00 - 0.00)
Diarrhea	23 (12.0)	0.00 (0.00 - 0.00)	18 (11.3)	0.00 (0.00 - 0.00)	5 (15.6)	0.00 (0.00 - 0.00)
Total score (x ± s)	24.35 ± 10.32		26.01 ± 9.93		16.09 ± 8.15	

Note: The scores for all 34 symptoms surveyed do not conform to a normal distribution.

Table 2. Additional symptom item scores for lung cancer patients treated with immune checkpoint inhibitors.

Symptom Items	Containing ICIs (n = 191)		ICIs Combined with Other Treatments (n = 159)		ICIs Monotherapy (n = 32)	
	Frequency/ Composition Ratio n/%	M (P25 - P75)	Frequency/ Composition Ratio n/%	M (P25 - P75)	Frequency/ Composition Ratio n/%	M (P25 - P75)
Skin pigmentation	21 (11.0)	0.00 (0.00 - 0.00)	21 (13.2)	0.00 (0.00 - 0.00)	0 (0.0)	0.00 (0.00 - 0.00)
Capillary proliferation	18 (9.4)	0.00 (0.00 - 0.00)	16 (10.1)	0.00 (0.00 - 0.00)	2 (6.2)	0.00 (0.00 - 0.00)
Gum bleeding	13 (6.8)	0.00 (0.00 - 0.00)	11 (6.9)	0.00 (0.00 - 0.00)	2 (6.2)	0.00 (0.00 - 0.00)
Weakness in both lower limbs	10 (5.2)	0.00 (0.00 - 0.00)	10 (6.3)	0.00 (0.00 - 0.00)	0 (0.0)	0.00 (0.00 - 0.00)
Chest tightness	9 (4.7)	0.00 (0.00 - 0.00)	8 (5.0)	0.00 (0.00 - 0.00)	1 (3.1)	0.00 (0.00 - 0.00)
Memory decline	9 (4.7)	0.00 (0.00 - 0.00)	3 (1.9)	0.00 (0.00 - 0.00)	1 (3.1)	0.00 (0.00 - 0.00)
Skin dryness and peeling	7 (3.7)	0.00 (0.00 - 0.00)	7 (4.4)	0.00 (0.00 - 0.00)	0 (0.0)	0.00 (0.00 - 0.00)
Stiffness in hands and lower limbs	4 (2.1)	0.00 (0.00 - 0.00)	4 (2.5)	0.00 (0.00 - 0.00)	0 (0.0)	0.00 (0.00 - 0.00)
Abdominal bloating	3 (1.6)	0.00 (0.00 - 0.00)	3 (1.9)	0.00 (0.00 - 0.00)	0 (0.0)	0.00 (0.00 - 0.00)
Increased appetite	3 (1.6)	0.00 (0.00 - 0.00)	3 (1.9)	0.00 (0.00 - 0.00)	0 (0.0)	0.00 (0.00 - 0.00)
Dry and gritty eyes	3 (1.6)	0.00 (0.00 - 0.00)	3 (1.9)	0.00 (0.00 - 0.00)	0 (0.0)	0.00 (0.00 - 0.00)
Tearing	3 (1.6)	0.00 (0.00 - 0.00)	3 (1.9)	0.00 (0.00 - 0.00)	0 (0.0)	0.00 (0.00 - 0.00)
Swollen and painful gums	2 (1.0)	0.00 (0.00 - 0.00)	2 (1.3)	0.00 (0.00 - 0.00)	0 (0.0)	0.00 (0.00 - 0.00)
Oral odor	2 (1.0)	0.00 (0.00 - 0.00)	2 (1.3)	0.00 (0.00 - 0.00)	0 (0.0)	0.00 (0.00 - 0.00)
Foreign body sensation in the eyes	1 (0.5)	0.00 (0.00 - 0.00)	1 (0.6)	0.00 (0.00 - 0.00)	0 (0.0)	0.00 (0.00 - 0.00)
Eye pain	1 (0.5)	0.00 (0.00 - 0.00)	1 (0.6)	0.00 (0.00 - 0.00)	0 (0.0)	0.00 (0.00 - 0.00)
Total score (x ± s)	1.01 ± 1.50		1.14 ± 1.58		0.34 ± 0.79	

3.2. Comparison of Treatment-Related Symptoms Experienced by Lung Cancer Patients with Different Characteristics

According to the normality test, all the physiological factors and social environment factors in this study did not conform to the normal distribution. Therefore, the rank sum test was used to analyze the data of different physiological factors, including gender, body mass index BMI and receiving treatment. The difference in treatment was statistically significant. The Kruskal-Wallis method was used for pairwise comparison between groups. Among the variables with statistically significant differences in **Table 3**, it was found that the symptom scores for females were significantly higher than for males ($P < 0.01$); patients with a BMI < 18.4 had higher symptom scores than those with a BMI ≥ 18.5 ($P < 0.05$); patients receiving ICIs combined with chemotherapy had significantly higher symptom scores than those receiving ICIs alone ($P < 0.01$); and patients with a monthly household income per capita < 2000 yuan had higher symptom scores than those with a per capita monthly income > 2000 yuan ($P < 0.01$).

Table 3. Comparison of treatment-related symptoms experienced by lung cancer patients with different characteristics (n = 191).

Item	Frequency	Total Symptom Score ($\bar{x} \pm s$)	Statistic	P
Gender				
Male	159	23.38 \pm 9.87	-2.60	0.009**
Female	32	29.19 \pm 11.30		
Age				
27-	10	27.50 \pm 8.20	1.19	0.552
40-	109	24.05 \pm 10.85		
60 - 84	72	24.38 \pm 9.80		
BMI (kg/m²)				
17.4 (Underweight) ①	5	38.00 \pm 14.27	3.53	0.016*
18.5- (Normal) ②	113	24.02 \pm 9.90		
23.9- (Overweight) ③	59	23.29 \pm 10.15		
27.9 - 31.1 (Obese) ④	14	26.64 \pm 10.34		
① > ②				0.017*
① > ③				0.013*
Diagnosis				
Non-small cell lung cancer	152	24.26 \pm 10.30	-0.22	0.828
Small cell lung cancer	39	24.69 \pm 10.56		
Course of disease (months)				
1-	101	24.77 \pm 10.02	6.53	0.088
6-	37	23.54 \pm 10.18		
12-	44	22.75 \pm 11.30		
36 - 67	9	30.78 \pm 7.65		

Continued

Tumor stage				
II	8	21.88 ± 7.85	2.60	0.273
III	44	22.05 ± 9.46		
IV	139	25.22 ± 10.63		
Current treatment				
Immunotherapy ①	32	16.09 ± 8.15	33.40	0.001**
Immunotherapy combined with chemotherapy ②	140	26.76 ± 9.66		
Immunotherapy combined with targeted therapy ③	9	19.44 ± 10.82		
Immunotherapy combined with targeted therapy and chemotherapy ④	10	21.40 ± 10.45		
② > ①				0.001**
Course of ICIs Treatment				
1-	143	25.21 ± 9.81	4.81	0.090
5-	37	21.62 ± 10.90		
10 - 20	11	22.36 ± 13.73		
Number of Concurrent Chronic Conditions				
0	132	23.68 ± 10.61	0.52	0.172
1	56	25.55 ± 9.71		
2	3	31.00 ± 5.29		
Karnofsky Score				
70-	2	20.00 ± 4.24	-0.76	0.448
80 - 100	189	24.40 ± 10.36		
Presence of Metastasis				
No	7	24.41 ± 9.16	-0.17	0.862
Yes	184	24.36 ± 10.39		
Degree of Clinical Remission				
Partial Remission (PR)	67	24.84 ± 9.45	2.42	0.298
Stable Disease (SD)	110	23.64 ± 10.93		
Progressive Disease (PD)	14	27.64 ± 9.27		
Education Level				
Middle school or below	110	23.69 ± 10.61	1.22	0.545
High school or technical school	45	25.55 ± 9.71		
College or above	36	31.00 ± 5.29		

Continued

Marital Status				
Married	180	30.70 ± 9.33	-1.63	0.102
Unmarried	11	24.03 ± 10.30		
Number of Children				
0-	49	26.96 ± 11.65	3.84	0.147
2	67	24.24 ± 9.91		
3 - 5	75	22.87 ± 9.62		
Primary Caregiver				
Spouse/Partner	133	24.69 ± 10.25	1.20	0.548
Parents/Children	36	24.94 ± 11.28		
Friends, Caregivers, or Self	22	21.32 ± 11.94		
Long-Term Residence				
Urban	139	24.80 ± 10.70	-0.93	0.354
Rural	52	23.27 ± 9.34		
Primary Occupation				
Farmer/Worker	52	24.88 ± 10.15	9.44	0.051
Company Employee	32	22.22 ± 10.64		
Public Institution Employee	32	24.13 ± 8.14		
Civil Servant	11	31.45 ± 8.05		
Self-Employed or Homemaker	64	23.88 ± 11.31		
Current Employment Status				
Employed	32	22.66 ± 8.56	3.09	0.378
Retired	71	25.62 ± 10.30		
Unemployed	61	24.64 ± 11.38		
On Leave	27	22.37 ± 9.71		
Household Per Capita Monthly Income (yuan)				
0- ①	15	31.73 ± 10.71	6.76	0.034*
2000- ②	98	24.06 ± 10.45		
5000- ③	78	23.37 ± 9.68		
① > ③				0.035*
② > ③				0.039*

Note: *: $P < 0.05$, **: $r < 0.01$.

3.3. Correlation of Coping Styles, Anxiety, and Depression with Symptom Scores

Patient symptom scores were positively correlated with the “acceptance-resignation” dimension of medical coping styles, anxiety, and depression, as detailed in **Table 4** and **Table 5**.

Table 4. Correlation between treatment-related symptoms and medical coping styles (n = 191).

Item	Total Symptom Score		
	Score (X ± S)	Correlation Coefficient (r)	P
Confrontation	17.29 ± 3.76	0.125	0.085
Avoidance	17.05 ± 2.77	0.108	0.136
Acceptance-resignation	9.55 ± 2.89	0.259	0.001**

Note: *: P < 0.01.

Table 5. Correlation between treatment-related symptoms and anxiety and depression (n = 191).

Item	Symptom Score		
	Score (X ± S)	r	P
Anxiety	3.61 ± 3.52	0.280	0.001**
Depression	6.26 ± 3.97	0.515	0.001**

Note: *: P < 0.01.

3.4. Multivariate Analysis of Influencing Factors on Symptoms in Lung Cancer Patients Treated with Immune Checkpoint Inhibitors

Using the total symptom score of lung cancer patients treated with immune checkpoint inhibitors as the dependent variable, variables with significant results in the univariate analysis and Pearson correlation analysis were used as independent variables. Dummy variables were assigned to multcategory variables and entered using the enter method, while other binary and quantitative variables were handled using the stepwise method to construct a multiple linear regression analysis model. The assignments of independent variables in the multiple linear regression model are shown in **Table 6**. The results of the regression analysis are shown in **Table 7**.

Table 6. Assignments of independent variables in the multiple linear regression model.

Variable	Assignment
Gender	Male = 1; Female = 2
BMI	Using 18.5-kg/m ² as a reference, set dummy variables: X1 = 17.4-kg/m ² (0, 1); X2 = 23.9-kg/m ² (0, 1); X3 = 27.931.1 kg/m ² (0, 1)
Current Treatment	Using ICIs monotherapy as a reference, set dummy variables: X1 = ICIs combined with chemotherapy (0, 1); X2 = ICIs combined with targeted therapy (0, 1); X3 = ICIs combined with chemotherapy and targeted therapy (0, 1)
Household Per Capita Monthly Income	Using 0 yuan as a reference, set dummy variables: X1 = 2000 yuan (0, 1); X2 = 500,060,000 yuan (0, 1)
Depression	Quantitative variables

Continued

Anxiety	Quantitative variables
Medical Coping Styles	Quantitative variables
Confrontation	Quantitative variables
Avoidance	Quantitative variables
Acceptance-resignation	Quantitative variables

Table 7. Multiple linear regression analysis of symptoms in patients with lung cancer treated with immune checkpoint inhibitors.

Item	Partial Regression Coefficient		Standardized Regression Coefficient Beta	t	P
	B	Standard Error			
Constant	5.224	4.268		1.224	0.223
BMI					
17.4-kg/m ²	12.597	3.796	0.195	3.318	0.001**
23.9-kg/m ²	0.421	1.358	0.019	0.310	0.757
27.9 - 31.1 kg/m ²	2.109	2.358	0.053	0.894	0.372
Current Treatment					
ICIs Combined with Chemotherapy	7.562	1.695	0.325	4.461	0.001**
ICIs Combined with Targeted Therapy	2.749	3.137	0.057	0.876	0.382
ICIs Combined with Chemotherapy and Targeted Therapy	6.868	3.005	0.149	2.285	0.023*
Depression	1.136	0.166	0.437	6.835	0.001**
Acceptance-resignation	0.399	0.162	0.145	2.457	0.015*

Note: The Durbin-Watson statistic is 1.804, $F = 12.422$, $P < 0.001^{**}$; $P < 0.05^{*}$; $P < 0.01$, Adjusted $R^2 = 0.375$.

4. Discussion

4.1. Current Status of Symptoms in Lung Cancer Patients Treated with Immune Checkpoint Inhibitors

Patients with lung cancer treated with immune checkpoint inhibitors bear a significant symptom burden. The most common symptoms include fatigue, decreased mental state, poor sleep quality, urinary abnormalities, loss of appetite, taste changes, dry mouth, cough, hair loss, itching, depression, skin changes, a feeling of fullness, decreased interest in sex, and pain. For patients receiving ICI monotherapy, the top five symptoms were fatigue, decreased mental state, dry mouth, poor sleep quality, and urinary abnormalities; for those receiving ICIs com-

bined with other treatments, the top five symptoms were fatigue, poor sleep quality, decreased mental state, loss of appetite, and urinary abnormalities.

In this study, the incidence of skin changes was 53.9%, and the incidence of skin itching was 57.1%. Skin changes mainly included itching, rash, pigmentation, dryness (peeling, flaking), and capillary hyperplasia. Previous researchers have considered skin changes to be mainly due to the skin toxicity of antitumor drugs [5] [15]. The incidence of symptoms in lung cancer patients treated with ICIs monotherapy and ICIs combined with other treatments is not entirely the same. Compared with combined treatment plans, patients receiving ICI monotherapy reported a lower incidence and severity of gastrointestinal symptoms such as nausea and vomiting, but more often reported skin symptoms such as rash and itching. Currently, for mild to moderate (grade 1 - 2) skin-related symptoms, clinical approaches typically involve the topical use of emollients, oral antihistamines, and/or topical medium-potency corticosteroids for symptomatic treatment [5] [16] [17]. More severe (grade 3 - 4) skin symptoms are rare and generally require the suspension of ICI treatment and active treatment with high-potency corticosteroids topically, or consultation with dermatology experts and systemic corticosteroid therapy [5] [16] [17].

In this study, among the symptoms reported by patients, the presence of Reactive Cutaneous-Capillary Endothelial Proliferation (RCCEP) showed a statistically significant difference with the use of the immune checkpoint inhibitor drug Camrelizumab ($\chi^2 = 144.258$, $P < 0.01$). Patients treated with Camrelizumab exhibited scattered “red mole” type spots or “tumor-like” growths on the facial area, head and neck, and trunk. Patients commonly self-assessed the severity as grade 1 - 2, and these spots were prone to rupture with difficult bleeding control after rupture. Therefore, patients using Camrelizumab should be informed in advance that RCCEP might appear on the skin surface during the first cycle after the initial drug administration (2 - 4 weeks). RCCEP is rarely observed on oral and nasal mucosa and generally will self-resolve or persist until 1 - 2 months after drug cessation. This information can prevent patients from experiencing undue anxiety [17]-[19]. For patients with RCCEP, careful observation and patient education are essential. Patients should be informed that RCCEP is prone to rupture and uncontrollable bleeding, so they should wear soft clothing and avoid scratching or rubbing the affected area. In cases of bleeding, applying pressure or using Yunnan Baiyao powder can help stop it. For “tumor-like” RCCEP lesions that affect daily life, laser treatment or surgical removal may be performed [18] [19].

4.2. Factors Influencing Symptoms in Lung Cancer Patients Treated with Immune Checkpoint Inhibitors

In the multiple linear regression analysis of this study, the physiological factors influencing patient symptoms with statistical significance were BMI and the current treatment method. Psychological factors included depression and the “acceptance-resignation” dimension of medical coping styles.

4.2.1. Physiological Factors

1) Body Mass Index (BMI)

BMI directly reflects the nutritional status of patients. In this study, there were statistically significant differences in symptoms among patients with different BMI levels. Patients with a BMI of 17.4 - 18.5 kg/m² were included in the multiple linear regression equation, indicating that underweight patients had a higher incidence or more severe symptoms, consistent with previous studies [20] [21]. Research on lung cancer patients shows that underweight and obese patients have higher postoperative complications compared to those with normal BMI, and the functional and nutritional status of patients influences the prognosis and quality of life [20]-[24]. The better the basic physiological and nutritional condition of patients, the higher their tolerance to tumors and antitumor treatments [22] [25]. Therefore, in clinical practice, patients with a BMI outside the normal range, especially those below the normal level, should receive nutritional interventions, such as guidance on a high-protein, easily digestible diet, and, if necessary, oral nutritional supplements like protein powder. This helps maintain a normal BMI, enhancing tolerance to antitumor treatments and reducing symptom occurrence and progression [26] [27].

2) Current Treatment Method

The results of this study indicate that the treatment plan is an important predictor of total symptom score. Compared to ICIs monotherapy and ICIs combined with targeted therapy, patients receiving ICIs combined with chemotherapy and ICIs combined with chemotherapy and targeted therapy had higher total symptom scores. This is because chemotherapy for lung cancer patients is highly toxic, the chemotherapy cycles are generally long, and most undergo long-term maintenance chemotherapy, which has been associated with more severe symptoms as the duration increases [6] [28] [29]. In the univariate analysis, the current treatment method had a statistically significant difference with total symptom scores ($P < 0.01$). Inter-group comparisons showed statistical significance in total symptom scores between ICIs combined with chemotherapy and ICIs monotherapy and between ICIs combined with targeted therapy ($P < 0.05$), suggesting that the overall symptoms of ICIs combined with chemotherapy patients are more severe than those treated with ICIs monotherapy or ICIs combined with targeted therapy, consistent with current research findings [29]. Therefore, there should be an emphasis on the prevention and management of symptoms in patients receiving ICIs combined with chemotherapy.

4.2.2. Psychological Factors

1) Coping Styles

Coping styles are a cognitive appraisal between stressors and behavioral interventions, affecting people's response types and intensity to stressful events, and regulating their adaptation processes and outcomes. Positive adaptive coping styles have a beneficial impact on health outcomes, whereas maladaptive negative coping styles negatively affect individuals' health outcomes. It has been reported

that postoperative lung cancer patients adopting negative coping styles are more prone to depressive symptoms [30]; lung cancer patients using positive coping styles have higher quality of life levels and perceive less pain, with acceptance-resignation coping styles having the greatest impact on comfort levels during chemotherapy [31]. An optimistic coping style is significantly negatively correlated with cancer-related fatigue in breast cancer patients, while emotional and fatalistic negative coping styles are significantly positively correlated with fatigue in cognitive dimensions [32].

The results of this study found that acceptance-resignation is a predictor of total symptom scores ($P < 0.05$), with more severe treatment-related symptoms found in those using acceptance-resignation coping styles. Acceptance-resignation is a common negative emotional coping style among cancer patients, characterized by a pessimistic and hopeless attitude towards the disease, believing they cannot control its progression, avoiding communication with medical staff, and eventually abandoning treatment compliance (e.g., not taking medication on time, refusing rehabilitation activities), even falling into self-blame and self-pity. This coping style is not merely a “negative emotion” but adversely affects symptom management by reducing treatment adherence, increasing psychological burden, lowering quality of life, and diminishing psychological resilience, thus seriously impacting patients’ health outcomes [33]-[36]. In clinical practice, psychological interventions (such as cognitive behavioral therapy, relaxation training, group psychotherapy) are needed to help patients change their coping styles and develop positive coping strategies (e.g., confronting, seeking support) to improve their health outcomes [37] [38].

2) Depression

This study found that depression is a risk factor for the severity of symptoms in lung cancer patients. The higher the depression score, the higher the total symptom score, which is consistent with previous research [39]-[41]. As one of the common negative emotions in cancer patients, depression, as a psychological factor, affects patients’ perception and experience of the disease and symptoms. Patients with higher levels of depression are more sensitive to symptom perception and experience, often manifesting through somatization [42] [43]. Depression exacerbates the symptom burden in lung cancer patients through multiple mechanisms. On one hand, depression can lead to immune function suppression (such as inducing apoptosis of immune cells and inhibiting antigen presentation), worsening the body’s inflammatory response to tumors, thereby exacerbating physical symptoms like pain and dyspnea [39] [40] [44]. On the other hand, the negative emotions of depressed patients (such as anxiety and hopelessness) create a vicious cycle of “low mood → less willingness to cooperate with treatment → symptom deterioration.” Depressed patients may abandon regular treatment (e.g., missing medication, refusing rehabilitation training), leading to tumor progression or unmanaged treatment side effects (e.g., nausea, hair loss from chemotherapy), thereby increasing the symptom burden [44] [45]. Additionally, depression can lower the

pain threshold, making patients more sensitive to physical symptoms like pain, further amplifying symptom perception. In clinical practice, it is important to emphasize depression screening and intervention for lung cancer patients [46]. Early identification of depressive symptoms and timely psychological (such as cognitive-behavioral therapy or supportive psychotherapy) or pharmacological interventions (such as antidepressants) can improve patients' emotional states and alleviate their symptom burdens (such as somatic symptoms and lung cancer-specific symptoms), enhancing quality of life [39].

5. Conclusion

In summary, patients with lung cancer treated with immune checkpoint inhibitors bear a significant symptom burden, with the most common symptoms being fatigue, decreased mental state, poor sleep quality, urinary abnormalities, loss of appetite, taste changes, dry mouth, cough, hair loss, itching, depression, skin changes, bloating, decreased sexual interest, and pain. Compared to monotherapy with ICIs, patients receiving ICIs combined with other treatments experience more severe symptoms (higher total symptom scores). The symptoms of lung cancer patients treated with ICIs are influenced by BMI, the type of treatment received, depression, and negative coping styles. A limitation of this study is that it is a cross-sectional survey, which does not allow for a longitudinal comparison of symptoms in lung cancer patients treated with ICIs at different stages. Future research could involve longitudinal studies to dynamically explore whether symptom levels change at different treatment stages and whether treatment duration affects symptom incidence and levels. This study was conducted in only one hospital, limiting the representativeness of the sample. Future research should involve multicenter studies to gather more data on the influencing factors and risk factors of symptoms in lung cancer patients treated with ICIs. By summarizing these risk factors, a warning model can be established for better prevention and management.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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