Symptom Experience of Lung Cancer Patients Treated With Immunotherapy Combined with Chemotherapy: A Longitudinal Study

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Abstract

The study aims to determine the incidence, frequency, severity, and distress of symptoms in lung cancer patients during the treatments with immune checkpoint inhibitors（ICIs） combined with chemotherapy, evaluating the characteristic of symptoms over time. This study used convenience sampling to select lung cancer patients who initially received a combination of ICIs and chemotherapy drugs in tertiary hospitals in Beijing from October 2023 to January 2025. The study instrumentsincluded a self-designed patient general information questionnaire and a Chinese version of the Memory Symptoms Assessment Scale (MSAS-Ch). Patients’ general information was collected before treatment, and symptom follow-up began on day 8 after the first treatment (T1), continuing until day 8 after the sixth treatment (T6). During this period, the incidence, frequency, severity, and distress level of symptoms were recorded. A total of 402 patients were initially included in the baseline measurements, with 43 dropouts, data from 354 patients was analyzed finally. 17 symptoms were extracted as the top ten most frequent occurrences during treatment. Fatigue, drowsiness, loss of appetite, altered taste, and nausea had an incidence >30% and consistently ranked in the top ten. A total of 15 symptoms scored ≥3 points (indicating "frequent" or "persistent") throughout the entire cycle. Fatigue, drowsiness, loss of appetite, and pain remained relatively frequent. In the T5, loss of appetite was the most frequent symptom (26.55%), while in the T6, pain was the most frequent (35.88%). Sixteen symptoms were rated as severe (≥3 points, indicating "serious" or "very serious"). Drowsiness and loss of appetite were consistently rated as more severe. In the assessment of the top ten symptoms rated as significant (≥3 points, indicating "moderately" or "severely"), only drowsiness persisted across all six cycles. The most prominent symptom was fatigue from T1 to T4 and T6 periods (37.29% to 50.85%). In the T5 period, hair loss (24.85%) and pain (23.45%) were the most distressing symptoms. Lung cancer patients exhibit various symptoms after receiving immunotherapy combined with chemotherapy. Over time, the incidence of perceived symptoms such as "fatigue and drowsiness" is higher than that of dietary-related symptoms like "loss of appetite and altered taste." These symptoms are most frequent, extremely severe, and cause significant distress. Health care providers can intervene during treatment to improve the patient's symptom experience by addressing symptoms that occur frequently or frequently, are more severe in perception, and are more troubling to the patient.

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1 Introduction

Lung cancer is the most common type of cancer worldwide and the leading cause of cancer-related deaths. In 2022, lung cancer accounted for approximately 12.4% of all new cancer cases and 18.7% of all cancer deaths globally(Bray F et al., 2024). In 2022, lung cancer ranked first among the top ten most common cancers in China(Han B et al., 2022), with about 1.06 million new cases and 730,000 deaths. The five-year survival rate was only 28.7%, and the prognosis for advanced lung cancer is poor(Zeng H et al., 2024). The treatment methods for lung cancer patients mainly include surgical resection, radiotherapy, chemotherapy, and immunotherapy. Recent studies(Zhou C et al., 2021; Zhou C et al., 2023; Reck M et al., 2024; Zhang S et al., 2023) have found that immunotherapy drugs represented by immune checkpoint inhibitors (ICIs), such as PD-1 and PD-L1 inhibitors, can significantly extend the long-term survival rate of patients, greatly reducing the treatment-related psychological burden and family economic burden(Liu Y., 2024). It was suggested as one of the standard treatment strategies. Moreover, the combination of immunotherapy and chemotherapy can produce a synergistic anti-tumor effect. The mechanism lies in that chemotherapy can enhance the immunogenicity of tumor cells, eliminate immunosuppressive factors, and regulate immune responses, thereby strengthening the efficacy of immunotherapy. At the same time, immunotherapy can improve the resistance of tumor cells to chemotherapy drugs, effectively enhancing the therapeutic effect of chemotherapy drugs and reducing their toxic and side effects. Therefore, the combination of immune inhibitors and chemotherapy has become an increasingly common treatment method in clinical practice.

Symptom experience refers to the frequency, severity, and distress level of symptoms perceived by individuals, as well as the significance of these symptoms in their generation and expression. A study reviewed the symptom profiles of patients with non-small cell lung cancer (NSCLC) treated with ICIs combined chemotherapy, finding that patients experienced fatigue, nausea, rash, itching, and pneumonia most prominently(Chen XM., 2023). Other researchers also identified four types of symptom experiences in lung cancer patients receiving immunotherapy combined with chemotherapy: perceived symptom distress, complex psychological feelings, diverse impacts, and inner expectations and needs(Li JP et al., 2023). Lung cancer patients experience various concurrent symptoms during treatment, which interact to form symptom clusters, significantly affecting patient prognosis and quality of life.

Currently, studies on the symptoms and symptom clusters of patients receiving chemotherapy combined with immunotherapy predominantly use the Anderson Symptom Assessment Scale (MDASI) and the Memory Symptom Assessment Scale (MSAS). A few studies are conducted through qualitative interviews. Clinical trials focusing on the combination of immunotherapy and chemotherapy drugs concentrate on safety and efficacy, with fewer longitudinal symptom studies and a lack of long-term follow-up research on patient symptom changes.

This study assessed lung cancer patients’ symptoms who were initially treated with immune checkpoint inhibitors (ICIs) combined with chemotherapy drugs, and further evaluate the longitudinal changes of their symptoms through four dimensions: incidence, frequency, severity and distress, and provide a basis for clinicians and nurses to improve patient symptom management.

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2 Methods

2.1 Patients and Settings

This prospective longitudinal study aimed to investigate the symptom experience of lung cancer patients during their six treatment cycles with immune checkpoint inhibitors combined chemotherapy.

The inclusion criteria for this study are: ①Patients clinically diagnosed with primary lung cancer (including small cell lung cancer and non-small cell lung cancer); ②Age over 18 years old and aware of their condition; ③ Never received any immunotherapy, or had a history of immunotherapy but at least 6 months since the last immunotherapy; ④Expected survival time exceeding 6 months; ⑤Conscious and able to communicate normally, capable of completing the questionnaire independently and willing to participate in this study. Exclusion criteria are as follows: ①Patients with other serious illnesses, critical conditions that prevent further treatment, or other malignant tumors; ② Patients participating in clinical trials; ③ Patients who have recently experienced major trauma, cognitive impairment, or severe mental illnesses. Elimination criteria are as follows: ① Patient prematurely discontinued the use of immunotherapy or chemotherapy drugs (such as due to surgery, changing the treatment plan due to disease progression, or reducing the dosage due to improved condition, etc.); ②Patient failed to complete the pre-set follow-up period or key time point data was missing and could not be supplemented due to transfer to another hospital, death, loss of contact, or voluntary withdrawal, etc; ③ Patient's responses were determined to be not taken seriously, with logical contradictions or low credibility. . These patients were recruited from the inpatient departments of the Department of Respiratory Medicine at Peking Union Medical College Hospital and the Cancer Hospital of the Chinese Academy of Medical Sciences from October 2023 to January 2025. The sample size was estimated based on the maximum number of items used in the scale, which should be 5 to 10 times the number of items. The clinical symptom questionnaire for this study includes 32 symptom items, so the sample size should be at least 160-320 cases.

After obtaining the consent and assistance of the relevant departments of lung cancer, the social demographic and clinical data of the patients who met the inclusion criteria were collected on the day of planned immunotherapy combined with chemotherapy (T0). The symptom manifestations of the patients were followed up on the 8th day after the first treatment (T1), with an interval of 21 days as one cycle, for a total of six consecutive cycles (T1-T6). The researchers conducted one-on-one follow-ups via phone or We Chat. Before the patients were discharged and recovered at home after the treatment, the scales used to assess the symptoms after treatment were sent to the patients in advance to help the subjects familiarize themselves with the content and filling norms of the scales, so that they could review the symptoms after treatment.

2.2 Instruments

This study utilized a self-designed general information questionnaire for patients to investigate their sociodemographic data (gender, age, average monthly family income, educational level, marital status, and employment status) and clinically relevant data (height, weight, histological type of lung cancer, stage, comorbidities, smoking history, drinking history, medication history, family history, immunotherapy regimens, and duration of chemotherapy).

To comprehensively investigate patients ' symptoms and identify symptom clusters, this study adopted the Chinese version of the Memory Symptom Checklist (MSAS-Ch), assessing patients' symptom experiences within one week after treatment. The Memory Symptom Checklist (MSAS) was developed by the American Sloan-Kettering Cancer Center and translated into Chinese by Cheng in 2007 (MSAS-ch) (Cheng K.K et al., 2009) . It is used to evaluate the incidence,

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frequency, severity, and distress level of 32 symptoms over the past week in cancer patients. The scale consists of two parts. The first part covers the first 24 symptoms, with scores calculated as the average of the frequencies, severities, and distress levels. The second part includes the last 8 symptoms, with scores based on the average of the severity and distress levels. Frequency and severity are scored using a 4-point Likert scale, while distress level uses a 5-point Likert scale. The internal consistency coefficient Cronbach's α for the Chinese version of the Memory Symptom Checklist ranges from 0.79 to 0.87, with content validity at 0.94 and structural validity ranging from 0.68 to 0.79, indicating good reliability and validity.

2.3 Data Privacy

This study strictly adheres to ethical guidelines and implements stringent confidentiality measures for data from lung cancer patients receiving immune checkpoint inhibitor combination chemotherapy. All patient information is processed using an anonymous coding method to ensure patient privacy and security. Before conducting the survey, patients 'informed consent is fully obtained, and the purpose, procedures, and risks of the study are explained in detail. The principle of fairness is upheld throughout, providing all participants with uniform data collection standards and questionnaire content to avoid any impact on research results due to information discrepancies. The principle of benefit over harm is strictly observed, minimizing the potential burden on patients' physical and mental health as much as possible. If patients experience discomfort during the survey, they can request to pause or terminate the study at any time.

2.4 Data Analysis

The SPSS software was used for data analysis. For normally distributed continuous variables, mean ± standard deviation was adopted; for skewed continuous variables, median and quartile were used; categorical variables were described using frequencies and percentages.

3 Results

This study included a total of 402 patients in the baseline. 5 patients were excluded due to inaccurate responses to questionnaire questions during telephone follow-ups. 16 cases changed their medication regimen due to disease progression, and 12 cases underwent neoadjuvant surgery during treatment; 11 cases discontinued medication due to severe adverse reactions, including 5 for severe pneumonia, 1 for immune-related myocarditis, and 5 for immune-related skin adverse reactions.4 patients failed to complete follow-up due to long treatment duration and loss of contact. Ultimately, 354 patients were included in this study.

3.1 Demographic Data of Lung Cancer Patients

A total of 354 lung cancer patients ranged in age from 34 to 85 years, with an average age of (63.65 ± 9.99) years. Among them, 272 were male (76.84%), and 82 were female (23.16%). The highest proportion had completed junior high school (43.79%), followed by those with high school or vocational education (29.94%). The majority (40.11%) had a monthly household income between 3,000 to 6,000 yuan, while the second largest group (16.95%) had an income between 6,000 to 10,000 yuan. The marital status was predominantly married, at 96.33%, while only 29.94% were employed (Table 1).

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Table 1. Demographic data of patients (n=354)

Category	Number of cases (cases)	Composition Ratio (%)
Gender		
Male	272	76.84
Female	82	23.16
Employment Status		
Employed	106	29.94
Not Employed*	248	70.06
Marital Status		
Married	341	96.33
Single	9	2.54
Divorced or Bereaved	4	1.13
Monthly Per Capita Income (Yuan)		
<3000	129	36.44
3000～6000	142	40.11
6000～10000	60	16.95
>10000	13	3.67
Education		
Primary School and Below	60	16.95
Junior High	155	43.79
Senior High or Technical Secondary School	106	29.94
Higher Vocational or Bachelor's Degree and Above	33	9.32

*: Not Employed includes retirees, unemployed, and other work-inactive statuses.

3.2 Clinical Data of Lung Cancer Patients

Among the 354 patients, BMI 16.02~34.01kg/m2, normal individuals (18.5~23.9) accounted for 47.46%; 78.25% had a history of smoking, and 66.38% had a history of alcohol consumption; 56.78% were in good physical condition (PS=0),57.91% had comorbidity, and 38.14% had a family history of cancer. Adenocarcinoma (47.74%) and squamous cell carcinoma (39.55%) were the predominant subtypes, with 93.22% being stage III or IV patients. The main immunotherapy

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drugs used were pembrolizumab (41.81%) and tislelizumab (34.18%), while carilizumab, sintilimab, and other immunotherapeutic agents accounted for about 24%; the primary chemotherapeutic agents used in combination were etoposide, albumin-bound paclitaxel, and platinum-based drugs (Table 2).

Table 2. Patient Clinical Data (including treatment) (n=354)

Category	Number of cases (cases)	Composition Ratio (%)
Smoking History		
None	77	21.75
Yes	277	78.25
History of Alcohol Consumption		
None	119	33.62
Yes	235	66.38
BMI(kg/m2)		
<18.5	12	3.39
18.5-23.9	168	47.46
24.0-27.9	149	42.09
≥28.0	25	7.06
TNM Stage		
Stage I + Stage II	24	6.78
Stage III + Stage IV	320	90.4
Family History		
None	219	61.86
Yes	135	38.14
Previous Treatment History		
None	188	53.11
Yes	166	46.89
Chronic Disease History		
None	149	42.09
Yes	205	57.91
Pathological Type		
Squamous Cell Carcinoma	140	39.55

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Adenocarcinoma	169	47.74
Small Cell Carcinoma	24	6.78
Other Types of Cancer	21	5.93
ECOG PS (Score)		
0	201	56.78
≥1	153	43.22
Drug Treatment Plan		
Pembrolizumab Combined with Chemotherapy	148	41.81
Tislelizumab Combined with Chemotherapy	121	34.18
Carrrelizumab Combined with Chemotherapy	22	6.21
Sintilimab Combined with Chemotherapy	21	5.93
Other ICIs Combined with Chemotherapy	42	11.86

3.3 Lost-to-Follow-Up Information of Lung Cancer Patients

A total of 43 lung cancer patients failed to complete the 6-cycle follow-up. Among the 43 lost-to-follow-up patients, the oldest was 80 years old and the youngest was 41 years old; the maximum BMI was 28.70 kg/m² and the minimum was 17.65 kg/m² . Compared with the 354 lung cancer patients who completed the follow-up, there were statistically significant differences between the two groups of lung cancer patients in seven categories: average monthly income per capita of the family, ECOG PS score, history of chronic diseases, previous treatment history, smoking history, pathological classification, and occupational status ($P<0.05$) (Table 3).

Table 3. Comparison of Differences between Lung Cancer Patients with Completed and Incompleted Follow-up

Variable	Follow-up completed group (n = 354)		Follow-up incomplete group (n=43)		χ^2	*P-value*
	Number of cases (cases)	Percentage (%)	Number of cases (cases)	Percentage (%)		
Monthly Per Capita Income (Yuan)						
<3000	129	36.44	4	11.76	26.891	0
3000～6000	142	40.11	8	23.53		
6000～10000	60	16.95	12	35.29		

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>10000	23	6.5	10	29.41		
ECOG PS (score)						
0	201	56.78	0	0	135.769	0
1	130	36.72	3	8.82		
2	18	5.08	10	29.41		
3	5	1.41	21	61.76		
Chronic disease history						
None	149	42.09	6	17.65	7.726	0.005
Yes	205	57.91	28	82.35		
Previous treatment history						
None	188	53.11	27	79.41	8.293	0.013
Yes	166	46.89	7	20.59		
Smoking history						
None	77	21.75	13	38.24	4.731	0.03
Yes	277	78.25	21	61.76		
Pathological type						
Squamous cell carcinoma	140	39.55	19	55.88	12.883	0.03
Adenocarcinoma	169	47.74	7	20.59		
Small cell carcinoma	24	6.78	2	5.88		
Other types of cancer	21	5.93	6	17.65		
Occupational status						
Employed	106	29.94	4	11.76	5.047	0.025
Not Employed	248	70.06	30	88.24		

3.4 Changes in the top 10 Incidence of Symptoms in Patients with Lung Cancer During T1-T6 Cycles

The MSAS-Ch scale was used to evaluate 32 symptoms of patients, and the top 10 symptom types in each cycle were extracted. A histogram was drawn with the time points of 6 cycles as the horizontal axis and the incidence of symptoms as the vertical axis.

During the T1 to T6, a total of 17 symptoms were extracted, among which fatigue, drowsiness, loss of appetite, altered taste, Restless sleep, Nausea had an incidence rate >30%, consistently ranking in the top ten symptoms. During the T1, the incidence rates of fatigue, drowsiness, loss of appetite, Cough, altered taste were as high as 50%, while the incidence rate of these five symptoms (Feeling sad, Anxiety, Irritability, Nausea, Constipation) was >40%. In the T2, new symptoms of Restless sleep (40.96%) and Pain (37.85%) were added, with the incidence rates of Feeling sad and Anxiety decreasing compared to the T1. In the T3, the highest incidence rate of Anxiety (84.75%) was followed by fatigue (81.92%) and Looking unlike oneself (78.53%), with the addition of Weight loss (42.09%). During the T4, the incidence rate of Weight loss (41.65%) ranked first, and this period also saw the addition of Itchy skin (41.65%) and Hair loss (37.57%). In the T5 and T6, the incidence rate of drowsiness (66.10%~67.51%) was significantly higher than that of fatigue (46.05%~47.18%), with only pain having an incidence rate >50% in the T5, and both drowsiness and Pain having an incidence rate >50% in the T6 (Figure 1).

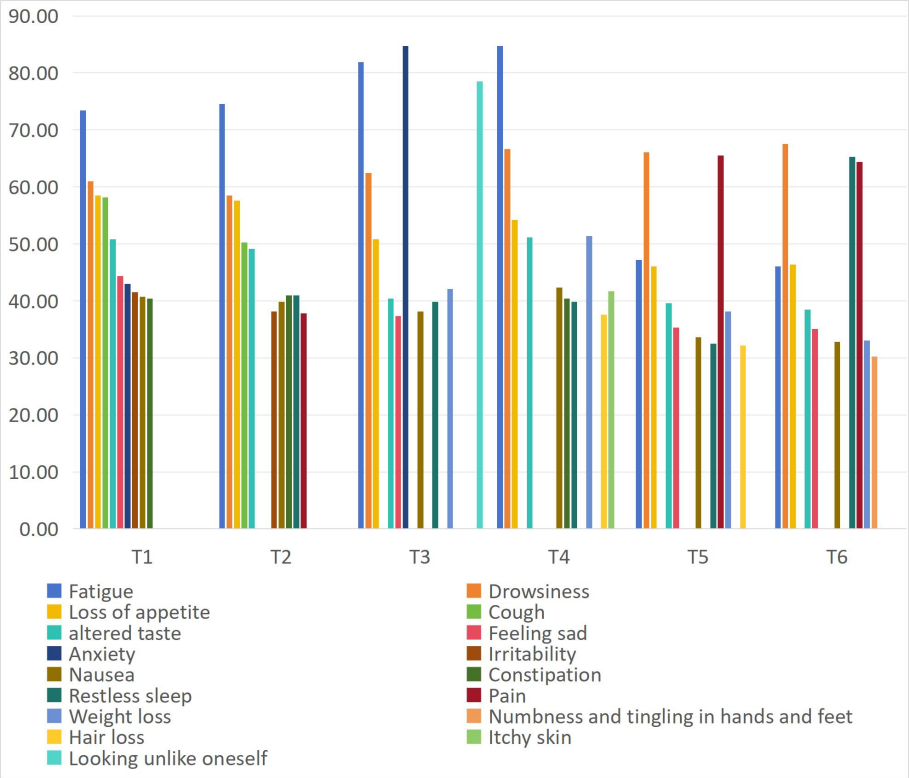

Figure 1. Top 10 symptoms of lung cancer patients during T1-T6

3.5 Changes in the top 10 Frequency of Symptoms in Patients with Lung Cancer During T1-T6 Cycles

Based on MSAS-Ch scale (24 symptoms in the first part), the symptom characteristics with a frequency score of 3 or more ("frequent" and "continuous occurrence") at T1-T6 were extracted and analyzed, and the frequency histogram of symptoms was drawn.

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During the T1 to T6, a total of 14 symptoms were extracted. Among these, fatigue, drowsiness, loss of appetite, and Pain consistently ranked in the top ten most frequent symptoms over six cycles. The symptom of fatigue was the most prevalent in the first four cycles, with the highest frequency in cycle T4 (54.52%) followed by T1 (50.28%). In the T5, loss of appetite (26.55%) was the most frequent, while in the T6, Pain (35.88%) was the most frequent (Figure 2).

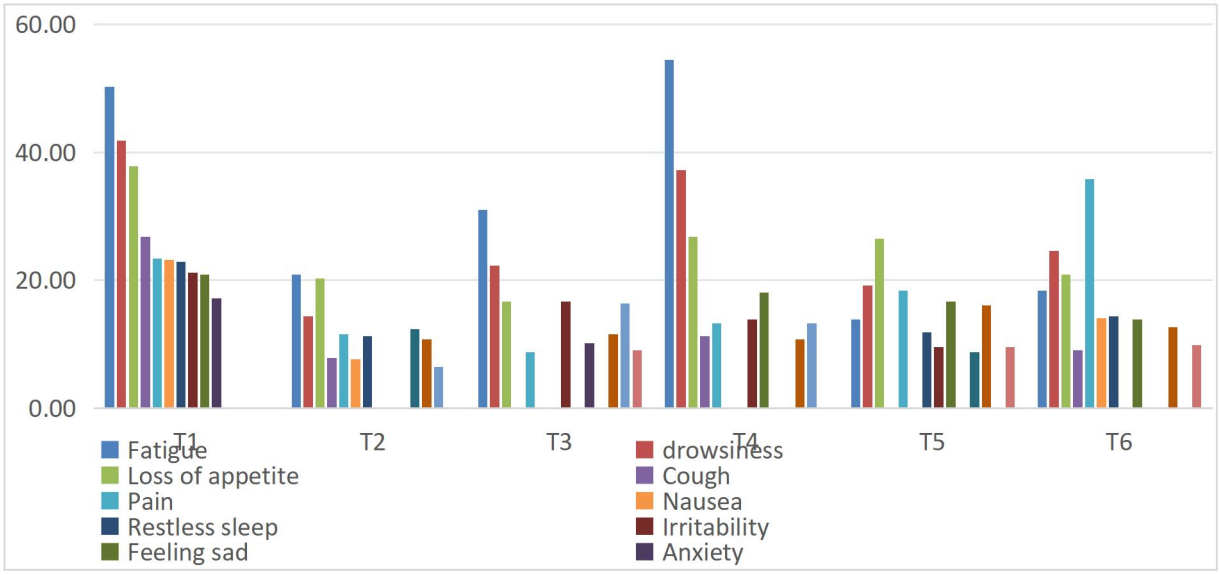

Figure 2. Top 10 symptoms with frequency score of ⩾3 in the T1-T6 for lung cancer patients

3.6 Changes in the top 10 Severity of Symptoms in Lung Cancer Patients During T1-T6 Cycles

The MSAS-Ch scale was used to evaluate 32 symptoms of patients, and the top ten symptom characteristics with a severity score of ≥3 ("serious" and "very serious") in each cycle were extracted and analyzed, and the histogram of symptom severity was drawn.

During the T1 to T6 cycles, a total of 16 symptoms were extracted, with drowsiness and loss of appetite consistently ranking in the top ten most severe symptoms over six cycles. Symptoms such as fatigue (44.07% to 55.37%), drowsiness (34.18% to 45.20%), and loss of appetite (29.66% to 36.72%) remained relatively severe throughout the first four cycles; drowsiness (31.07% to 39.27%) was the most severe in the last two cycles. In cycle T5, loss of appetite (27.12%) and Hair loss (26.27%) were more severe, while in cycle T6, Pain (37.85%) and loss of appetite (24.86%) were more severe (Figure 3).

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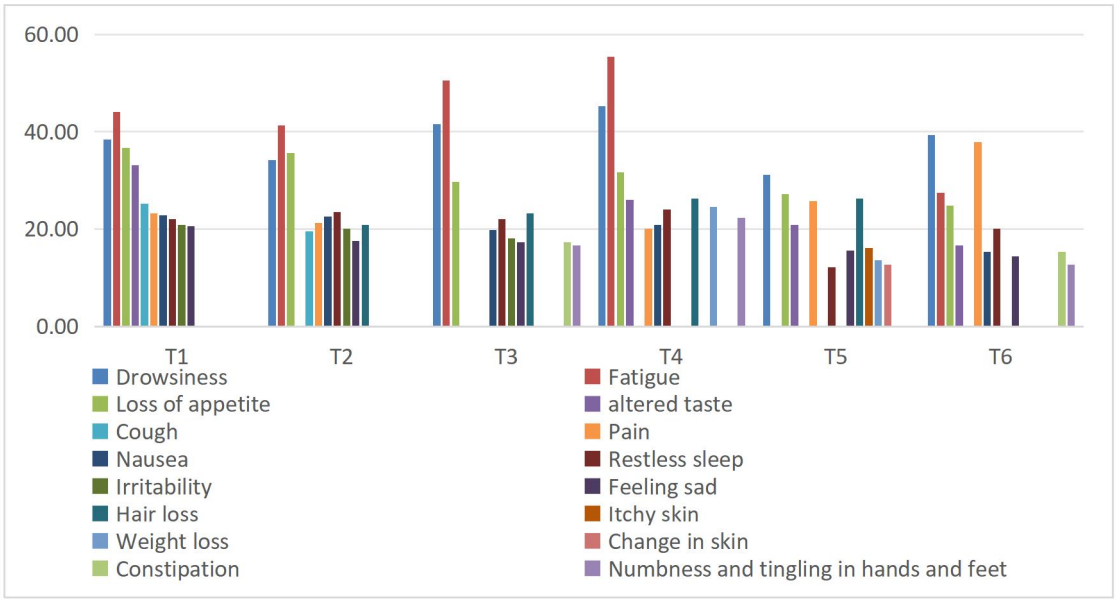

Figure 3. Top 10 symptoms with severity score of ≥3 in the T1-T6 for lung cancer patients

3.7 Changes in the top 10 Distress of Symptoms in Lung Cancer Patients During T1-T6 Cycles

The MSAS-Ch scale was used to evaluate 32 symptoms of patients, and the top ten symptom characteristics with significant distress scores of ≥3 ("large" and "very large") in each cycle were extracted and analyzed, and the histogram of symptom distress was drawn.

A total of 16 symptoms were extracted from the T1 to T6 cycles, with drowsiness consistently ranking among the top ten most troubling symptoms in six cycles. Among these, fatigue was the most prominent in the T1 to T4 and T6 periods (37.29% to 50.85%), while hair loss (24.85%) and pain (23.45%) were the most distressing in the T5 period (Figure 4).

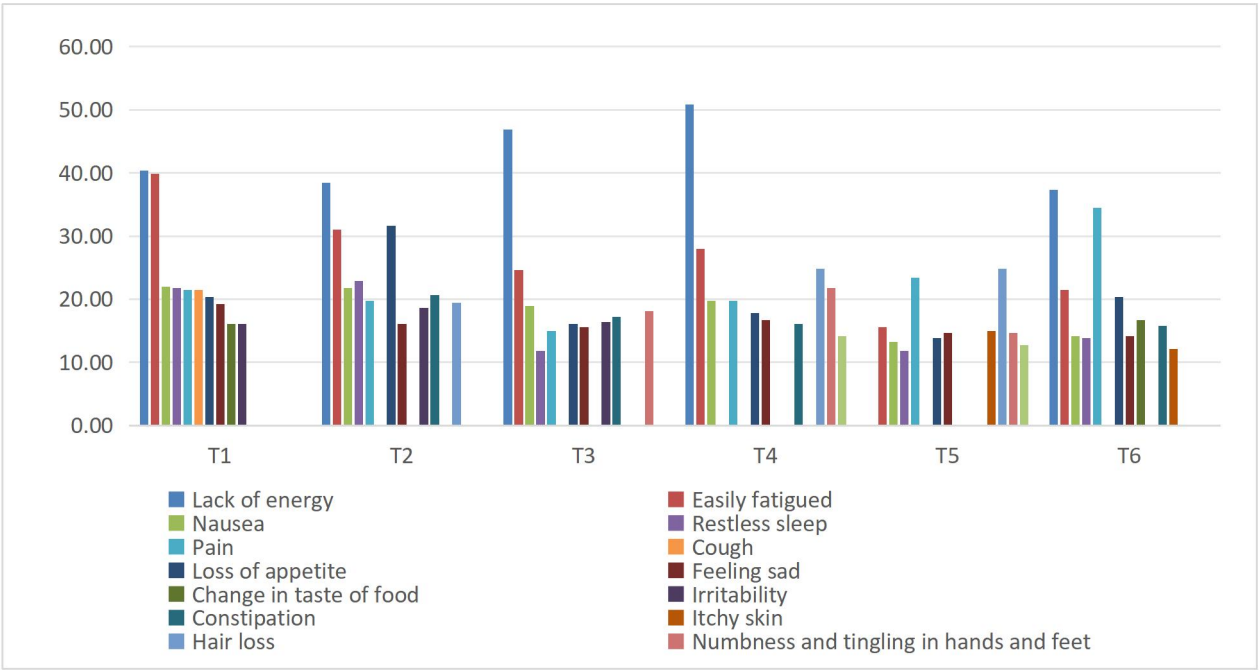

Figure 4. Top 10 symptoms with distress score of ≥3 in the T1-T6 for lung cancer patients

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4 Discussion

4.1 General Data Analysis of Lung Cancer Patients

This study's results on the 354 lung cancer patients included show that the proportion of males (76.84%) is significantly higher than females, with a male-to-female ratio of 3.3:1, which aligns with many previous epidemiological studies on lung cancer, indicating that males remain a high-risk group for lung cancer(Bray F et al., 2024). This is mainly because the smoking rate among men is generally higher than that among women, and smoking is one of the main risk factors for lung cancer. The average age of lung cancer patients is (63.65 ± 9.99) years, predominantly married (96.33%), unemployed (70.06%), and middle-to-low-income (76.55% of households with a monthly income ≤ 6000 yuan). Moreover, 84.74% of patients have an education level of junior high school or below, suggesting that the burden of lung cancer may be closely related to socioeconomic status. The high proportion of elderly patients (average age 63.65 years) and the high rate of unemployment (70.06%) indicate potential risks of declining physical condition or comorbidity in this study population. The main pathological types of patients in this study are adenocarcinoma (47.74%) and squamous cell carcinoma (39.55%), consistent with the pathological characteristics of lung cancer in Asian populations(Han B et al., 2022). Chen surveyed the pathological characteristics of 992 lung cancer patients between 2014 and 2018, finding that the proportions of adenocarcinoma and squamous cell carcinoma were 57.86% and 31.85%, respectively, with the proportion of adenocarcinoma increasing over time, while the proportion of squamous cell carcinoma decreased(Chen GB et al,. 2021). The high smoking rate among lung cancer patients (78.25%) and the late diagnosis rate (93.22%) highlight the urgency of strengthening tobacco control campaigns and early screening. In terms of drug selection, pembrolizumab has the highest usage rate in immune checkpoint inhibitor (ICI) therapy (41. 81%), which may be related to the coverage of health insurance and the recommended intensity of clinical guidelines. Tislelizumab, as an independently developed PD-1 inhibitor in China, was included in the national health insurance directory in 2021. It is currently widely used as a first-line or second-line recommended regimen for NSCLC. The combination chemotherapy regimen primarily involves pemetrexed plus platinum and albumin-bound paclitaxel plus platinum, in line with the first-line treatment standards for advanced lung cancer(Ettinger DS et al., 2023).

4.2 Differences between Lost-to-Follow-Up and Followed-Up Patients with Lung Cancer

In the group that did not complete the follow-up, the proportion of high-income individuals (with an income of over 10,000 yuan) was relatively higher. This might be due to the fact that high-income people have busy work schedules and fast-paced lives, making it difficult for them to spare time for follow-up visits. Patients with an ECOG PS score of 3 had the highest proportion, and those with a history of chronic diseases accounted for as high as 57.91%. Patients in poor physical condition might be unable to undergo long-term treatment due to the severity of their illness or have longer hospital stays, which could exhaust their energy and make it hard for them to complete follow-ups on time. Patients' insufficient understanding and awareness of their disease, along with a lack of long-term contact and communication with the medical system, have led to a lack of awareness and habit of cooperating with medical follow-ups. Therefore, patients without a history of previous treatment in the group that did not complete the follow-up (79.41%) were more likely to fail to complete the follow-up, and smokers (61.76%) tended to have looser management of their health behaviors and poorer compliance, making it relatively more difficult for them to complete the follow-up. On the other hand, employed individuals might be more dependent on medical insurance and other benefits, and thus are more willing to maintain good communication with the medical system to obtain better medical services, resulting in a relatively higher proportion of follow-up completion. In the group that did not complete the follow-up, the proportion of patients with squamous cell carcinoma was relatively higher. Squamous cell carcinoma often originates in larger bronchi, and the tumor stimulates the bronchial mucosa,

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easily causing irritating dry cough and other symptoms. This might affect the patients' sleep quality, disrupt their work and rest, and further induce anxiety about their illness, thereby affecting their psychological state in participating in follow-ups.

4.3 Comparison of Symptom Characteristics in Six Cycles of Immunotherapy Combined with Chemotherapy in Lung Cancer Patients

The symptoms of "drowsiness, fatigue and loss of appetite" are extremely significant. During the combined immunotherapy and chemotherapy treatment for lung cancer patients, the incidence, frequency, severity, and distress level of drowsiness symptoms consistently rank in the top ten throughout the entire cycle; all patients experience the highest incidence of fatigue symptoms during cycles T1 to T4, with significant symptom experiences. Cancer-related fatigue is the most common accompanying symptom in cancer patients. The National Comprehensive Cancer Network defines cancer-related fatigue (CRF) as a subjective feeling caused by cancer itself or cancer treatment, primarily manifesting as physical, emotional, and/or cognitive fatigue or exhaustion(NCCN, 2020). This symptom is characterized by its painful and persistent nature, making it the most prevalent accompanying symptom in cancer patients. During active cancer treatment, the incidence of CRF ranges from 62% to 85%, with moderate to severe cases accounting for 30% to 60. CRF can occur throughout the entire course of cancer, characterized by persistent fatigue lasting more than two weeks, often accompanied by cognitive impairment and low mood, and hindering daily life, which is consistent with the earlier finding that the incidence of drowsiness was only slightly lower than that of fatigue.

Persistent loss of appetite is characterized by a high incidence rate, frequent and severe symptoms, but the level of distress felt is not intense. This may be due to the fact that the treatment drugs have not yet caused significant gastrointestinal adverse reactions such as nausea and vomiting, and the patient’s positive expectations for treatment outcomes may have alleviated subjective discomfort to some extent. During chemotherapy, lung cancer patients experience many dietary issues, such as poor appetite and loss of taste. Appetite, as a subjective physiological and psychological sensation that drives food intake, manifests as reduced or absent hunger perception, premature satiety after eating, and partial or complete loss of eating desire. This decrease in appetite can lead to insufficient nutrient intake, resulting in malnutrition and even cachexia, which severely impacts health(Chinese Society for Nutritional Oncology of China Anti-Cancer Association et al., 2022). Zhang found through qualitative interviews with lung cancer patients during chemotherapy that dietary difficulties caused by chemotherapy reactions and loss of taste control significantly affect the nutritional status of patients, potentially influencing whether to continue the treatment regimen(Zhang Y.Y et al., 2023). Xu discovered that lung cancer patients undergoing chemotherapy lack proper nutritional knowledge, have limited access to nutritional information, and require high-quality dietary guidance(Xu X.N et al., 2020). Therefore, healthcare providers should thoroughly assess the nutritional awareness and needs of lung cancer patients, promptly provide personalized health education, encourage good eating habits, enhance self-management of diet, and improve the quality of life and clinical outcomes for patients.

During the T1-T2 treatment cycle, the incidence and frequency of physical symptoms (drowsiness, fatigue, loss of appetite) in lung cancer patients were significantly higher than that of psychological symptoms (irritability, Feeling sad, anxiety).

The severity and distress of "Pain and Hair loss" changed dynamically in the later stages of treatment. The incidence of pain in patients during the T5 cycle (65.54%) is relatively high, and symptoms occur more frequently in the T6 cycle, with significant scores for severity and distress. Peng conducted a 6-month symptom follow-up on 114 lung cancer patients undergoing their first immunotherapy, using a growth mixed model to identify three trajectories of pain changes(Peng N.N et al., 2023). The results showed that the severity of pain remained mild to moderate throughout, consistent with the findings of this study. The study found that treatment duration

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(OR=0.112, P=0.015) and the use of pemetrexed (OR=3.210, P=0.027) were factors influencing pain during immunotherapy. Wang compared short-term immunotherapy with chemotherapy in advanced lung cancer patients and found that patients in the short-term immunotherapy group had better pain control and lower rates of adverse reactions (P<0.05) (Wang Q et al., 2023). Pain is more frequent in patients during the T5 and T6 cycles, possibly due to primary tumor infiltration, metastatic site-related pain, or treatment-induced neuropathy. It is recommended to promptly assess pain outcomes in lung cancer patients and tailor pain management interventions based on a programmed pain management approach(Chen Z.M et al., 2024).

Patients in the T5 cycle experience severe hair loss and significant distress. Chemotherapy-induced hair loss refers to the partial or complete loss of hair from normal growth areas due to chemotherapy drugs killing tumor cells, affecting areas such as hair, eyebrows, eyelashes, armpit hair, and pubic hair(Ren Y.M et al., 2024). Chemotherapy is the treatment method with the highest rate of hair loss(Yang H et al., 2020). Previous studies indicate that over 70% of cancer patients consider hair loss a major psychological burden, and chemotherapy-induced hair loss causes patients to experience symptoms of image fixation and social barriers(Yang H et al., 2020; Xiao X.T et al., 2022; Gao R et al., 2023). Before treatment, preventive psychological interventions should be provided to patients, explaining in detail the reversibility of hair loss and recommending chemotherapy drugs with lower hair loss risk based on actual needs and condition permitting. At the same time, patients can use physical protective measures such as scalp cooling techniques. Clinical staff should encourage and guide patients to wear wigs and other image management tools, and support brief periods of emotional avoidance.

For the first time, this study utilized multi-cycle longitudinal tracking to demonstrate that drowsiness persisted as the most severe and troubling issue for patients even after six treatment cycles. This finding highlights the enduring nature of the burden imposed by chronic symptoms and underscores the particular clinical significance of symptoms like drowsiness during later stages of treatment. The study recommends that future efforts should focus on monitoring and addressing symptoms such as fatigue and drowsiness more closely, with timely detection and intervention aimed at further enhancing patients' quality of life.5 limitations

This study has certain limitations. The research subjects were confined to lung cancer patients seeking treatment in Beijing. The convenience sampling method has restricted its representativeness. In the future, it is necessary to carry out multi-center investigations and large - scale longitudinal studies. Meanwhile, attention should be paid to symptom clusters and core symptoms to thoroughly explore the characteristics of symptom evolution during the long - term immunotherapy of lung cancer patients. This will provide a basis for deciphering the mechanism of symptom occurrence and formulating targeted intervention strategies.

Moreover, this study merely conducted a cross-sectional comparison of symptoms in four dimensions after patients received treatment, without conducting a detailed analysis of the differences in symptom frequency and severity. It is suggested that subsequent research should enhance the comparison of symptoms across different dimensions.

The study has revealed that during the disease progression or treatment period, patients are more prone to develop eating disorders characterized by "loss of appetite" and systemic symptoms such as "fatigue". This might be associated with the metabolic consumption of the tumor and the accumulation of drugs. Notably, immune-related symptoms did not manifest significantly in the subjective experiences of patients. This could be attributed to the fact that the study did not employ follow-up scales specific to immune checkpoint inhibitors and lacked dynamic monitoring methods, resulting in the failure to detect potential immune-related adverse reactions in a timely manner.

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5 Conclusion

This study, through follow-up observation and analysis of 354 lung cancer patients who received immune checkpoint inhibitors combined with chemotherapy, identified five symptoms: drowsiness

fatigue, loss of appetite, altered taste, and nausea, consistently ranking in the top ten throughout the treatment period. The four most common symptoms were fatigue, drowsiness, loss of appetite, and pain; drowsiness and loss of appetite consistently ranked as severe symptoms, with drowsiness remaining the most troubling issue for patients over six cycles.

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