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Original Article

Negative correlations of psychological distress with quality of life and immunotherapy efficacy in patients with advanced NSCLC

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Abstract: To evaluate the relationships between psychological distress and immunotherapy efficacy, adverse reactions and quality of life scores in patients with advanced non-small cell lung cancer (NSCLC). A total of 104 NSCLC patients who received 4-6 cycles of standard immunotherapy were enrolled and evaluated with the Distress Thermometer (DT) and European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30). The aim was to analyze the correlation between psychological distress and quality of life and to analyze whether psychological distress affects the efficacy of and adverse reactions to immunotherapy. The objective response rate (ORR) and disease control rate (DCR) of the psychological distress group were 6% and 50%, respectively, and those of the no psychological distress group were 18.5% and 83.3%, respectively. The differences were statistically significant (χ^2=14.131, P<0.05). The progression-free survival (PFS) of advanced NSCLC patients who received comprehensive immunotherapy and had no psychological distress was significantly better than that of the psychological distress group (HR, 0.338; 95% CI, 0.192-0.592; P<0.05). The PFS of advanced NSCLC patients who received immunotherapy combined with chemotherapy in the no psychological distress group was significantly better than that in the psychological distress group (HR, 0.458; 95% CI, 0.296-0.709; P<0.05). Psychological distress in advanced NSCLC patients affects the efficacy of immunotherapy, and psychological distress is negatively correlated with quality of life during immunotherapy.

Keywords: Psychological distress, immunotherapy, non-small cell lung cancer, quality of life

Introduction

Lung cancer has become the main cause of cancer-related morbidity and mortality worldwide [1]. The 2-year survival rate for patients with non-small-cell lung cancer (NSCLC) increased by 8% from diagnosis in 2015-2016 compared with diagnosis in 2009-2010, with absolute increases of 5% to 6% for every stage of diagnosis [1]. Studies have found that compared with patients with other types of cancer, lung cancer patients have significantly greater psychological distress [2]. Psychological distress is an unpleasant emotional experience that is affected by many factors, including psychological factors (cognition, behavior and emotion), social factors and spiritual factors. It is a broad term that mainly manifests itself as anxiety, stress, worry, panic and fear. Some studies have shown that due to the particular characteristics of lung cancer, psychological distress has become an important factor affecting the quality of life of lung cancer patients [3].

Immunotherapy is one of the most important treatments for advanced NSCLC [4]. Immunotherapy can increase the survival of patients with advanced NSCLC, and the number of advanced NSCLC survivors is increasing [1]. The duration of response is the greatest advantage of immunotherapy, which can last for years once a response is obtained, and it can change the trajectory of the disease, even if the disease merely remains stable [5]. However, most patients who receive immunotherapy experience psychological distress. Currently, the psy-

chological distress experienced by advanced NSCLC patients has received increasing attention. Psychological distress is one of the most important factors affecting the quality of life of advanced NSCLC patients. Previous studies have found that the combination of anxiety, depression and other emotional factors during immunotherapy for advanced NSCLC is closely related to quality of life [6]. However, the effect of psychological distress on the efficacy of immunotherapy in these lung cancer patients remains unclear.

Chinese advanced NSCLC patients have different cultural backgrounds, lifestyles, and ways of thinking about the diagnosis and therapy of the disease than other populations of advanced NSCLC patients. The influence of psychological distress on the efficacy of immunotherapy and quality of life in advanced NSCLC patients receiving immunotherapy is still unclear. In this study, 104 advanced NSCLC patients who underwent immunotherapy were selected as the research subjects, and psychological distress and quality of life were measured in an attempt to determine whether the psychological distress experienced by advanced NSCLC patients affected the efficacy of immunotherapy and their quality of life.

Methods

Participants

Approximately 104 advanced NSCLC patients who met the inclusion criteria were selected from the tumor patients at the Second Affiliated Hospital of Anhui Medical University. There were 67 patients in the immunological combined chemotherapy group. The lung cancer patients were all treated at the Cancer Center of the Second Affiliated Hospital of Anhui Medical University from August 1, 2019, to January 31, 2021. Based on the Distress Thermometer (DT), the advanced NSCLC patients were divided into two groups without (DT<4) or with (DT≥4) psychological distress, and the groups were assessed for age, education level and other factors. The Research Ethics Committee of the Affiliated Second Hospital of Anhui Medical University approved the study (Number of Ethical Approval: 2012088), and all subjects signed informed consent forms.

The inclusion criteria for this study were as follows: 1. Pathologically confirmed NSCLC without previous immunotherapy; 2. Treatment with a dose, specific plan and timing of immunotherapy that were essentially the same as for the other patients and had a life expectancy longer than 6 months after treatment; 3. Karnofsky performance status (KPS) score >70, with normal speech and mental capacity and the ability to cooperate with the completion of immunotherapy and functional assessments; and 4. At least 18 years of age at diagnosis with adequate education and auditory/visual ability to complete the questionnaire.

The exclusion criteria for this study were as follows: 1. A diagnosis of depression, anxiety, dementia or other mental illnesses unrelated to cancer; 2. Fractures, cerebral infarction, or moderate or more severe cardiac insufficiency that seriously affected patient quality of life but were unrelated to the cancer; and 3. A diagnosis of other mental and physical diseases that affect quality of life.

Procedure

NSCLC patients were identified by prescreening inpatient tumor data, and qualified patients were recruited during hospitalization. The oncologist presented the study to each patient orally and obtained informed consent. The researchers then assessed each patient's ability to participate, performed baseline data collections and administered the questionnaires. The first questionnaire was given before immunotherapy. The EORTC QLQ-C30 questionnaire was completed before the start of immunotherapy and at the time of the first disease progression after treatment. After 2 cycles of treatment, the oncologist assessed the efficacy of the treatment against the Solid Tumor Efficacy Evaluation Criteria (RECIST), and after 2-3 cycles of treatment, the statistician performed the analysis on the collected data.

Measures

Evaluation of psychological distress: The Distress Thermometer (DT) is often used to assess patients' recent psychological stress. It is a single-item psychological distress rating tool first developed by Dr. Roth et al. It is scored from 0 to 10 (0 means no distress and 10 means extreme distress). The patient chooses

the number that best reflects the average level of distress level experienced over the past week. The recommended threshold for the identification of distress is 4 points. The Problem List (PL) was developed by the NCCN and consists of five subcategories: communication problems, practical problems, physical problems, emotional problems, and belief/religion problems. Some studies have shown that the DT has good accuracy and effectiveness for the assessment of clinical psychological distress.

Quality of life evaluation: The 30-item European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) was used to assess health-related quality of life (HRQoL) [7]. It contains five functional scales (role, physical, cognitive, emotional, and social functioning), a global QoL scale, three symptom scales (fatigue, nausea and vomiting, and distress), and six single items (appetite loss, diarrhea, dyspnea, constipation, insomnia, financial impact). The time frame of the questionnaire was one week, and a four-level answer format was adopted ("not at all", "a little", "quite a bit", and "very much"). There is a global quality of life scale, which has a seven-point response format. The score can be linearly converted to a score between 0 and 100 [8]. For the symptom scale, higher scores indicate worse symptoms. For the functioning and global QoL scales, a higher score indicates better health. The QLQ-C30 summary score is calculated as the mean of the combined 13 QLQ-C30 scale and item scores (excluding the global QoL and financial impact). The higher the score is, the better the HRQOL [9, 10]. The summary score was only calculated when all of the required 13 scales and item scores were available [11, 12].

Evaluation of the efficacy of immunotherapy: The Response Evaluation Criteria in Solid Tumors (RECIST) criteria were used to evaluate treatment efficacy. The criteria divide the evaluation of target lesions into complete response (CR) (all target lesions disappeared), partial response (PR) (30% reduction in the total length or diameter of baseline lesions), stable disease (SD) (the total length or diameter of baseline lesions decreased but did not reach PR or increased but did not reach PD), and progressive disease (PD) (20% increase in the total length or diameter of baseline lesions or new lesions). FPS was defined as the time from the beginning of immunotherapy to disease progression in patients with malignant tumors.

Doses of immunotherapy drugs: Five immunotherapy drugs were included in the study: Camrelizumab at 200 mg per dose, Sintilimab at 200 mg per dose, Pembrolizumab at 100 mg per dose, Atezolizumab at 1200 mg per dose, and Durvalumab at 600 mg per dose.

Statistical analysis

All data for this study are expressed as the means ± standard deviations. Statistical analysis was performed using SPSS Statistics software, to analyze the correlation between quality of life and psychological distress during immunotherapy. All statistical tests were double-tailed, and the significance level was set at $P<0.05$. Independent sample t tests and χ^2 tests were used to compare the differences in sample characteristics between groups at baseline. The scores in the psychological distress group and the no psychological distress group were compared using two independent samples t tests. A Cox regression analysis was performed to evaluate covariate associations with survival using censored data.

Results

Baseline demographics and clinical data

As seen in **Table 1** and **Figure 1**, 104 patients were divided by DT scale score (4-point threshold) into two groups, with 50 in the psychological distress group and 54 in the non-psychological distress group. There is no significant difference in demographic information, including age (t=1.018, P=0.311), sex (χ^2= 11.860, P=0.105), education (χ^2=17.285, P= 0.694), KPS (χ^2=11.735, P=0.110), pathological type (χ^2=0.166, P=0.683), tumor stage (χ^2=0.898, P=0.343), mutations (χ^2=1.001, P=0.606), methods of immunotherapy (χ^2= 30.230, P=0.352), immunotherapy drugs (χ^2=4.920, P=0.296) and number of tumor treatment lines (χ^2=1.781, P=0.411).

Comparison of therapeutic effect between groups with and without psychological distress

Table 2 shows the efficacy of immunotherapy in the psychological distress group. No patients

Table 1. Comparison of demographic characteristics and clinical data of NSCLC patients in the psychological distress group and the no psychological distress group

Characteristic	No PD (n=54)	PD (n=50)	T/χ^2	P
Age	64.44±10.39	66.50±10.17	1.018	.311
Sex, n (%)			11.860	.105
male	45 (83.3)	39 (78)		
female	9 (16.7)	11 (22)		
Education, n (%)			17.285	.694
illiteracy	8 (14.8)	12 (24)		
primary school	16 (29.6)	16 (32)		
middle school	21 (38.9)	20 (40)		
university	9 (16.7)	2 (4)		
Pathology, n (%)			0.166	.683
adenocarcinoma	27 (50)	23 (46)		
squamous cell carcinoma	27 (50)	27 (54)		
others	0 (0)	0 (0)		
Tumor stage, n (%)			0.898	.343
III	8 (14.8)	11 (22)		
IV	46 (85.2)	39 (78)		
Mutations, n (%)			1.001	.606
EGFR-	47 (87.0)	46 (92)		
EGFR+	4 (7.4)	3 (6)		
PD-L1+	3 (5.6)	1 (2)		
Methods of immunotherapy, n (%)			30.230	.352
1	10 (18.5)	4 (8)		
2	34 (63.0)	33 (66)		
3	9 (16.7)	9 (18)		
4	0 (0)	2 (4)		
5	1 (1.9)	2 (4)		
Immunotherapy drugs, n (%)			4.920	.296
Camrelizumab	39 (72.2)	39 (78)		
Sintilimab	7 (13.0)	8 (16)		
Pembrolizumab	5 (9.3)	0 (0)		
Atezolizumab	2 (3.7)	2 (4)		
Durvalumab	1 (1.9)	1 (2)		
KPS, n (%)			11.735	.110
80	25 (46.3)	30 (60)		
90	29 (53.7)	20 (40)		
Number of tumor treatment lines			1.781	.411
First-line treatment	24	26		
Second-line treatment	17	10		
Third-line treatment	13	14		

Abbreviations: PD: psychological distress group; Methods of immunotherapy: 1. Immunotherapy; 2. immunotherapy + chemotherapy; 3. immunotherapy + targeted therapy; 4. immunotherapy + radiation therapy; 5. immunotherapy + chemotherapy + targeted therapy; KPS: Karnofsky Performance Status.

reached a CR, 3 reached a PR, 22 had SD, and 25 had PD. In the no psychological distress group, no patients reached a CR, 10 reached a PR, 35 people had SD, and 9 had PD. The results were significantly different between the two groups (χ^2=14.131, P=0.001). **Table 3**

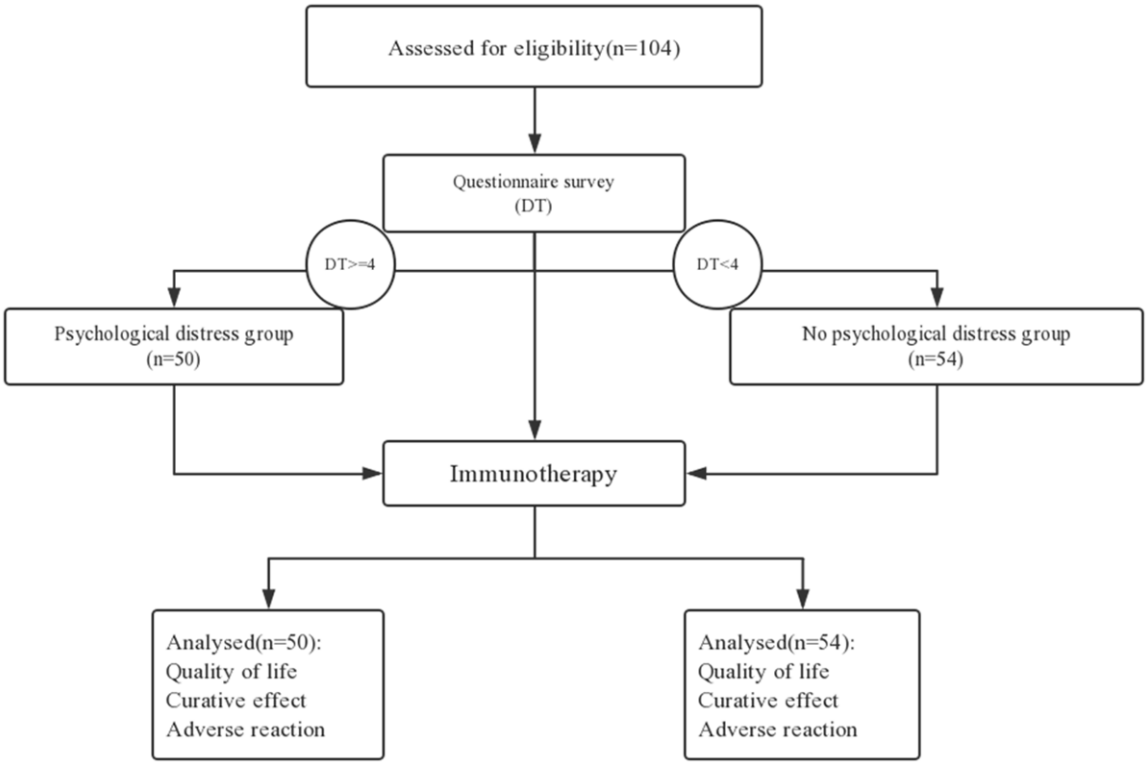

Figure 1. Flowchart of the study design, including the overall changes in participants. A total of 104 immunotherapy NSCLC patients was divided into two groups based on DT scale scores. Abbreviations: DT, Distress Thermometer.

Table 2. Comparison of the efficacy of immunotherapy in advanced NSCLC patients in the psychological distress group and no psychological distress group

Efficacy Outcome	No. (%)		X^2	P
	Psychological Distress Group (n=50)	No Psychological Distress Group (n=54)		
CR	0 (0)	0 (0)	14.131	.001
PR	3 (6)	10 (18.5)		
SD	22 (44)	35 (64.8)		
PD	25 (50)	9 (16.7)		

Abbreviations: CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease.

Table 3. Comparison of the efficacy of immunotherapy combined with chemotherapy in advanced NSCLC patients in the psychological distress group and no psychological distress group

Efficacy Outcome	No. (%)		X^2	P
	Psychological Distress Group (n=33)	No Psychological Distress Group (n=34)		
CR	0 (0)	0 (0)	9.026	.01
PR	2 (6.1)	6 (17.6)		
SD	14 (42.4)	22 (64.8)		
PD	17 (51.5)	6 (17.6)		

Abbreviations: CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease.

shows the efficacy of immunotherapy combined with chemotherapy in the psychological distress group. No patients reached a CR, 2 reached a PR, 14 had SD, and 17 had PD. In the no psychological distress group, no patients reached a CR, 6 reached a PR, 22 people had

Table 4. Influence of psychological distress on the quality of life of NSCLC patients during immunotherapy

	PD	No PD	t	P
N	50	54		
EORTC QLQ-C30 summary score (per 10 points) 1	79.68±10.31	89.48±6.09	-5.845	.000
EORTC QLQ-C30 summary score (per 10 points) 2	74.47±10.81	90.88±6.10	-9.431	.000

Abbreviations: PD: psychological distress group; EORTC QLQ-C30 summary score (per 10 points) 1: before immunotherapy; EORTC QLQ-C30 summary score (per 10 points) 2: after immunotherapy.

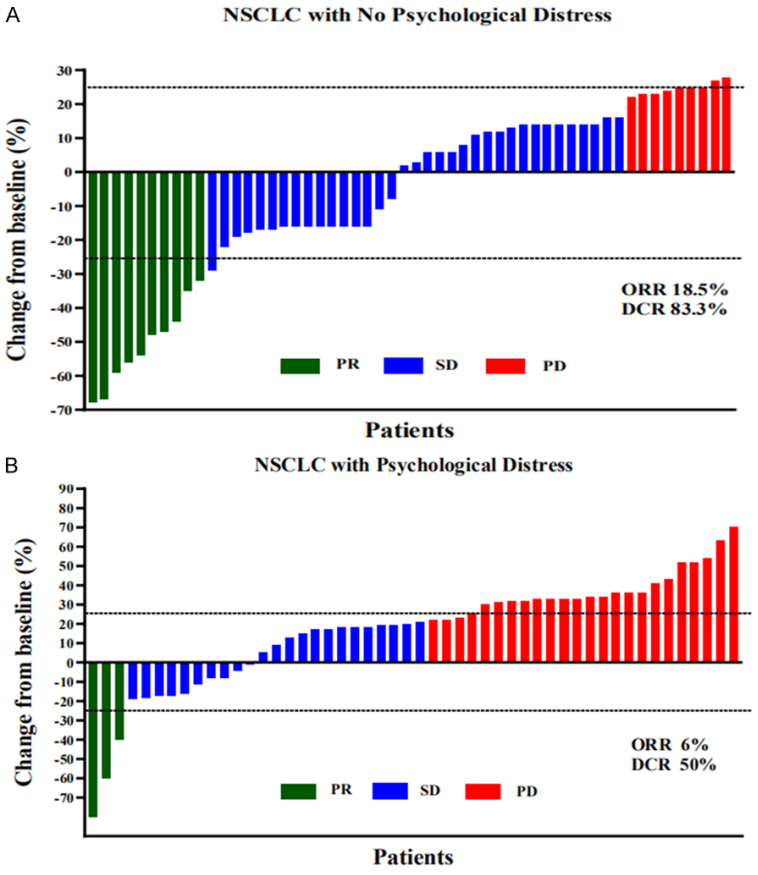

Figure 2. Correlation between psychological distress and immunotherapy efficacy in patients with advanced NSCLC. Abbreviations: Immunotherapy means all types of immunotherapy together, including combinations with targeted therapy, radiation and chemotherapy. A. No psychological distress group: ORR=18.5%, DCR=83.3%; B. Psychological distress group: ORR=6%, DCR=50%.

SD, and 6 had PD. The results were significantly different between the two groups (χ^2=9.026, P=0.01).

The correlation between psychological distress and quality of life

As shown in **Table 4**, before immunotherapy, the summary quality of life score of the 104 patients in the psychological distress group was 79.68±10.31 and that of the patients in the group without psychological distress was 89.48±6.09; the difference between the groups was statistically significant (t=-5.845, P=0.000<0.05). After immunotherapy, the summary score for quality of life in the psychological distress group was 74.47±10.81 points, and the summary score for quality of life in the group without psychological distress was 90.88±6.10 points; the difference between the groups was significant (t=-9.431, P=0.000<0.05). **Figure 4** shows that there was a negative correlation between the psychological distress score and the quality of life score in patients after immunotherapy. Data analysis in SPSS showed that the psychological distress score and quality of life score were significantly negatively correlated (r=-0.497, P=0.000).

The correlation between psychological distress and adverse events

Table 5 shows that both groups of advanced NSCLC patients were similar in the aspect of adverse events: the proportion of patients with hematologic syndromes in the psychological distress group was 10% and that in the group without psychological distress group was 7.4%. The proportion of patients with thyroid dysfunction in the psychological distress group was 2% and that in the group without psychological distress was 3.7%.

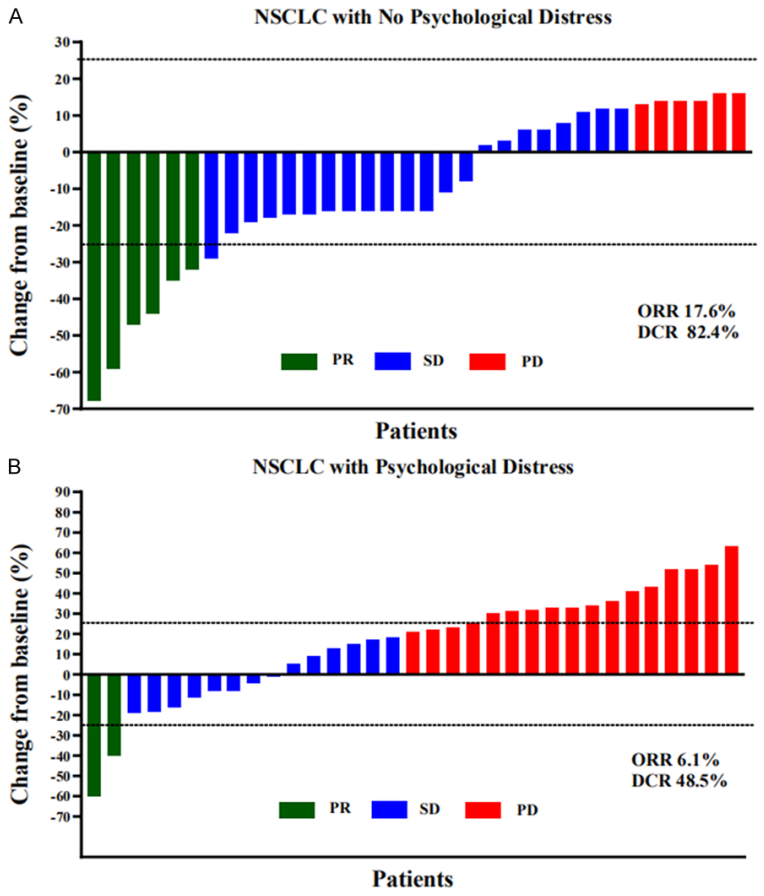

Figure 3. Correlation between psychological distress and immunotherapy combined with chemotherapy in patients with advanced NSCLC. Abbreviations: PR: partial response; SD: stable disease; PD: progressive disease. A. No psychological distress group: ORR=17.6%, DCR=82.4%; B. Psychological distress group: ORR=6.1%, DCR=48.5%.

ORR and DCR in patients receiving treatment

As shown in **Figure 2**, the objective response rate (ORR) and disease control rate (DCR) of the psychological distress group were 6% and 50%, respectively. The ORR and DCR were 18.5% and 83.3%, respectively, in the group without psychological distress. The ORR and DCR were significantly lower in the group with psychological distress than in the non-psychological distress group. In conclusion, the efficacy of immunotherapy was greater in the group without psychological distress than in the non-psychological distress group. As shown in **Figure 3**, in patients receiving immunotherapy combined with chemotherapy, the ORR and DCR in the psychological distress group were 6.1% and 48.5%, respectively. The ORR and DCR were 17.6% and 82.4%, respectively, in the group without psychological distress. The ORR and DCR were significantly lower in the group with psychological distress than in the group without psychological distress. In conclusion, the efficacy of immunotherapy combined with chemotherapy was better in the group without psychological distress than in the psychological distress group.

PFS in patients receiving treatment

As shown in **Figure 5**, the PFS of the advanced NSCLC patients who received comprehensive immunotherapy and had no psychological distress was significantly better than that of the psychological distress group (HR, 0.338; 95% CI, 0.192-0.592; P=0.00). As shown in **Figure 6**, the PFS of advanced NSCLC patients receiving immunotherapy combined with chemotherapy in the group without psychological distress was significantly better than that in the psychological distress group (HR, 0.458; 95% CI, 0.296-0.709; P=0.00).

Discussion

This study shows that psychological distress is one of the factors affecting the quality of life and prognosis of patients with advanced NSCLC receiving immunotherapy. We discovered that the ORR and DCR of patients with psychological distress were significantly lower than those of non-psychological distress patients. The PFS of advanced NSCLC patients with psychological distress was significantly lower than that of non-psychological distress patients. Meanwhile, the quality of life score of the psychological distress group was significantly lower than that of the non-psychological distress group. This controlled study suggests that psychological distress is related to quality of life, which is consistent with previous studies. We discovered a negative correlation between psycho-

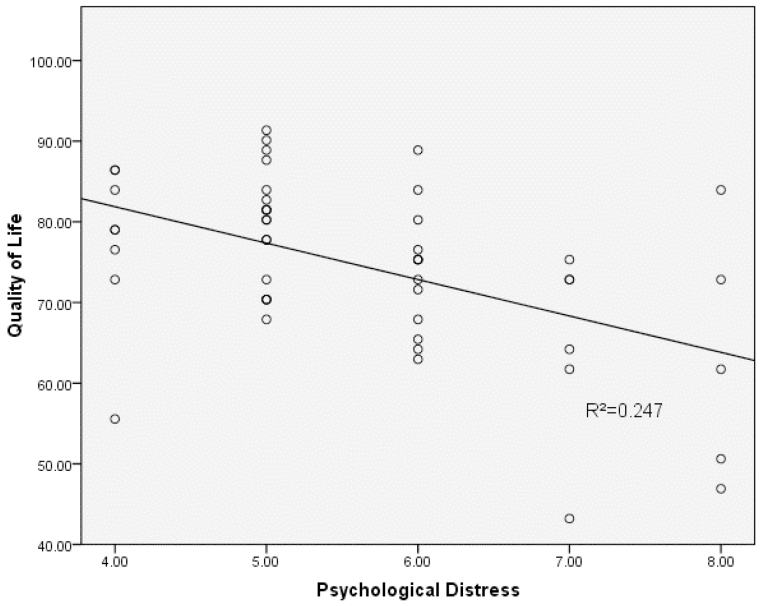

Figure 4. Relationship between psychological distress and quality of life after immunotherapy. The horizontal axis is the psychological distress score, and the vertical axis is the quality of life score; there is a negative correlation between them.

Table 5. Effects of psychological distress on adverse reactions during immunotherapy in patients with advanced non-small-cell lung cancer

Adverse event	N.%		χ^2	P
	PD (n=50)	No PD (n=54)		
Hematologic syndromes	5 (10)	4 (7.4)	0.221	.638
Immune-related dermatitis	13 (26)	7 (12.3)	2.841	.092
Immune-related pneumonitis	2 (4)	0 (0)	2.202	.138
Immune-related enteritis	3 (6)	0 (0)	3.336	.068
Thyroid dysfunction	1 (2)	2 (3.7)	0.269	.604
Others	3 (6)	1 (1.8)	1.208	.272

Abbreviations: PD: psychological distress group.

logical distress and quality of life in advanced NSCLC patients after immunotherapy.

Psychological distress is a multidimensional social, physical, emotional, and spiritual experience that can negatively impact a patient's ability to deal with cancer and its sequelae [13]. Many studies have reported high levels of psychological morbidity at different stages of a variety of cancer diagnoses [14, 15]. Some studies have indicated that the assessment of distress should be considered a "sixth vital sign". This means that monitoring emotional distress should be as important as monitoring other vital signs [16]. To monitor psychological distress, we usually use the DT. According to DT, many lung cancer patients experience psychological distress [17, 18].

The use of immunotherapy to treat malignant tumors was discovered by Dr. William B. Colley. The discovery of immunotherapy has prolonged the survival of advanced NSCLC patients and gradually increased the number of survivors [1]. Immunotherapy can not only enhance the immune response of T cells to tumors but also act on tumor-associated macrophages (TAMs), restore the phagocytosis ability of macrophages to tumors, inhibit tumor proliferation, and prolong the survival of patients [19]. For patients with NSCLC, immunotherapy can be combined with chemotherapy [20], targeted therapy, and radiotherapy [21]. Immunotherapy is influenced by many factors, such as psychological factors, the gut microbiome [22], cancer-associated fibroblasts (CAFs) [23, 24], hypoxia-induced factor 1α (HIF-1α) [25], adenosine A2a receptor (A2AR) [26, 27], and immune cells [28]. However, whether the efficacy of immunotherapy is influenced by psychological factors is not clear. Immunotherapy can lead to a wide variety of immune-related adverse events, and the most frequent immune-related adverse events are related to dermatologic toxicity [29, 30].

Immunotherapy in patients with NSCLC is associated with psychological distress and inflammation [5]. Initially, immunotherapy was thought to increase the risk of psychological distress through thyroid dysfunction or other mechanisms [31, 32]. Although psychological distress may be induced through mechanisms involving small-molecule inhibitors, it has been

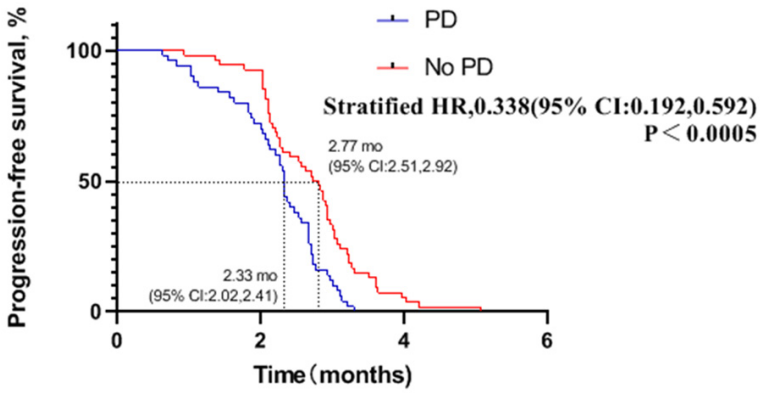

Figure 5. Progression-free survival in patients receiving immunotherapy for advanced non-small-cell lung cancer (overall), Abbreviations: PD: psychological distress group; immunotherapy means all types of immunotherapy together, including combinations with targeted therapy, radiation and chemotherapy.

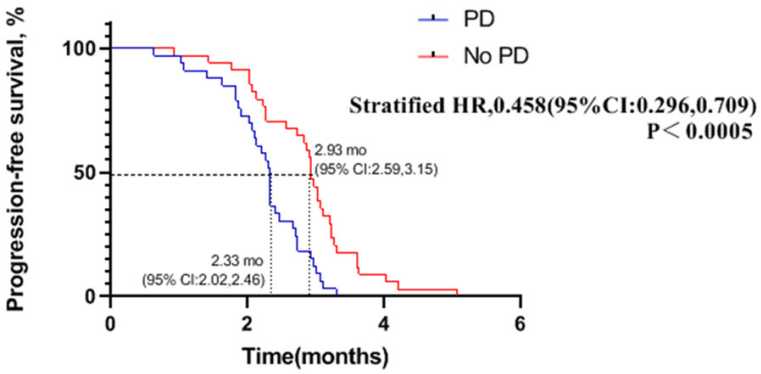

Figure 6. Progression-free survival in patients with advanced non-small-cell lung cancer receiving immunotherapy combined with chemotherapy (negative test results for EGFR). Abbreviations: PD: psychological distress group.

found that the incidence of psychological distress in patients receiving targeted therapy combined with immunotherapy is lower than that in patients receiving chemotherapy combined with immunotherapy [5]. In contrast, Jacobs et al. found that an elevated level of tumor necrosis factor α was associated with EGFR+ advanced NSCLC and reduced depression [31, 33]. However, some studies have found that patients with EGFR+ advanced NSCLC also have lower C-reactive protein (CRP) levels, which is consistent with the psychological distress via inflammation hypothesis [5]. Antidepressants may reduce the efficacy of immunotherapy , Capuron et al. [34] found that high doses of IL-2 and/or IFN-A during cancer immunotherapy can induce depressive symptoms that can be effectively descended with antidepressants, and explanatory of this phenomenon was that antidepressants may alter the production of endogenous cytokines induced by immunotherapy. Since socioeconomic status (SES) is known to influence cancer prognosis, the influence of socioeconomic status on the association between psychological distress and treatment types should also be considered [35]. According to existing studies, there is a complex relationship between smoking, inflammation and immunotherapy. However, this study did not involve the influence of smoking status on psychological outcomes, which should be further studied in the future [36]. Another problem is that these treatment categories will not change, but many treatments continue to evolve, and new treatment combinations have emerged; for example, immunotherapy combined with chemotherapy is already being used to treat patients with advanced NSCLC [20]. Different combinations of therapies will affect the efficacy of immunotherapy.

This study was the first to use the DT scale and the EORTC QLQ-C30 scale to evaluate the relationship between psychological distress and quality of life during immunotherapy in advanced NSCLC patients. This study has established a clear correlation between psychological distress and quality of life in patients with advanced NSCLC during immunotherapy, but there are still some shortcomings. This study was a small cross-sectional study. Large-sample and longitudinal studies are needed to determine the exact relationship between psychological distress and quality of life during immunotherapy.

Conclusion

In summary, our study provides direct evidence that psychological distress in advanced NSCLC

patients affects their quality of life during immunotherapy, providing a theoretical basis for improving the quality of life of advanced NSCLC survivors. At the same time, we found that psychological distress is one of the factors affecting the immunotherapy effect in patients with advanced NSCLC, providing a theoretical basis for improving the efficacy of immunotherapy in advanced NSCLC patients.

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Disclosure of conflict of interest

None.

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