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Original Article

Fear of cancer recurrence is related to the efficacy of immunotherapy and quality of life in patients with NSCLC during the COVID-19 pandemic in China

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Abstract: The outbreak of the COVID-19 pandemic has greatly impacted patients with non-small cell lung cancer (NSCLC), making the fear of cancer recurrence (FCR) more pronounced. We explored the effects of FCR on immunotherapy efficacy and quality of life during the COVID-19 pandemic in China among the 124 NSCLC patients enrolled in this study. Quality of life and immunotherapy efficacy were compared between high- and low-FCR groups after completing 4-6 courses of treatment or cancer progression. Worse immunotherapy efficacy and quality of life were reported for the high-FCR group than for the low-FCR group. These findings emphasize the need to pay close attention to the level of FCR in NSCLC patients. Efforts should be taken to alleviate FCR levels among NSCLC patients. Moreover, research is needed to investigate the possible link between immunotherapy efficacy and FCR.

Keywords: Immunotherapy, NSCLC, fear of cancer recurrence, quality of life

Introduction

Since the onset of the novel coronavirus disease (COVID-19) pandemic in China at the end of December 2019, the Chinese government has adopted strict procedures to control the epidemic, which have affected the treatment of tumor patients. Several guidelines for managing cancer patients during the pandemic have indicated the importance of maintaining patients' mental health [1, 2]. However, pandemics and treatment disruptions can increase the susceptibility of cancer patients to mental health declines, such as increased fears of cancer progression or recurrence.

Fear of cancer recurrence (FCR) is defined as any "fear, worry, or anxiety about the possibility of cancer recurrence or progression" [3], which manifests as a comprehensive negative psychological state. FCR is a common unmet need among cancer survivors [4]. Moderate to severe FCR often negatively affects patients' quality of life [5]. During the COVID-19 pandemic, FCR has become more pronounced among cancer patients due to disruptions in treatment planning [6]. However, most recent studies have focused on the relationship between FCR and quality of life among cancer survivors [7] or explored possible interventions, such as, the Internet-Based Mindfulness-Based Cognitive Therapy, the Blended Cognitive Behavior Therapy, and the ConquerFear [8-10], and few studies have investigated the impacts of FCR on overall treatment outcomes among cancer patients.

Lung cancer is a malignant tumor with the highest morbidity and mortality of all cancer types worldwide [11]. In recent years, the survival rate of patients with lung cancer has significantly improved due to advances in screening methods; improved understanding of cancer on the molecular, genetic, and immunological levels; and developments in personalized drugs [12].

However, advances in cancer treatment have been accompanied by increased examination exposures, higher numbers of treatment cycles, and longer follow-up times, which have resulted in lower quality of life among lung cancer patients than among patients with other cancer types [7]. Lung cancer patients are more negatively affected by mental and psychological aspects, and show higher risk of suicide [13], providing a potential foundation for the development and worsening of FCR.

Immunotherapy, especially the discovery and targeting of the programmed cell death 1 (PD-1)-programmed death ligand 1 (PD-L1) pathway, has profoundly changed the model for tumor treatment [14] and introduced the possibility of a "clinical cure" for the majority of tumor patients [15]. Prior studies have attempted to identify independent predictors of immunotherapy efficiency, examining genetic polymorphisms, the tumor microenvironment, and tumor molecular typing. Although various studies have explored the impacts of psychological factors on the immune system, the impacts of psychological factors on the outcomes of tumor immunotherapy are rarely examined.

To date, few studies have explored the impacts of FCR on immunotherapy efficacy and quality of life among patients with non-small cell lung cancer (NSCLC). The main objective of this research was to investigate whether high FCR is associated with worse immunotherapy efficacy and quality of life in patients with NSCLC.

Material and methods

Test design

This cohort study explored the effects of FCR on immunotherapy efficacy and quality of life among patients receiving immunotherapy for NSCLC. We collected baseline data from all participants at the time of study enrollment, including tumor size, quality of life scores, and Cancer Worry Scale (CWS) responses. Patients scoring ≥14 points on the CWS were classified as having high FCR, whereas patients scoring <14 points were classified as having low FCR. Tumor size and quality of life scores were also collected for all participants after they completed 4-6 courses of treatment or upon cancer progression. This research was approved by the Research Ethics Committee of the Second Affiliated Hospital of Anhui Medical University (Number of Ethical Approval: 2012088). All participants provided oral informed consent to participate in this study.

Participants

The inclusion criteria for participants included patients with (1) a diagnosis of adenocarcinoma, squamous cell carcinoma, and NSCLC other than adenocarcinoma and squamous cell carcinoma; (2) a soon-to-be-implemented treatment plan including immunotherapy drugs; (3) the ability to complete the CWS questionnaire independently or with assistance; (4) Karnofsky Performance Status (KPS) ≥80 points; and (5) life expectancy greater than 6 months. The exclusion criteria for participants included patients with (1) any history of severe mental illness, such as suicidal ideation, or any current mental illness; (2) changes in psychotropic medications within 3 months before baseline measurement or strong exposure events other than tumor diagnosis; and (3) other diseases that impact quality of life, such as severe heart failure or disability.

Program

Figure 1 shows the research flowchart. Participants were recruited from October 2020 to October 2021. All patients with NSCLC who were hospitalized in the Oncology Department of the Second Affiliated Hospital of Anhui Medical University (n=402) were assessed, and patients who were planned to receive comprehensive treatment, including immunotherapy (n=180), were identified. Informed consent for study enrollment was obtained in person or by phone (n=124). The CWS questionnaire was administered, and the results were used to categorize participants into either the high-FCR group (CWS≥14) or the low-FCR group (CWS< 14). Quality of life scores were assessed using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30), and lesion size data were also collected. Patients were followed until they completed 4-6 treatment courses or until disease progression, and quality of life scores and tumor size were collected during follow-up. Patients lost to follow-up were contacted by telephone to administer the EORTC QLQ-C30. The most recent hospitalization record was used to assess post-treatment tumor

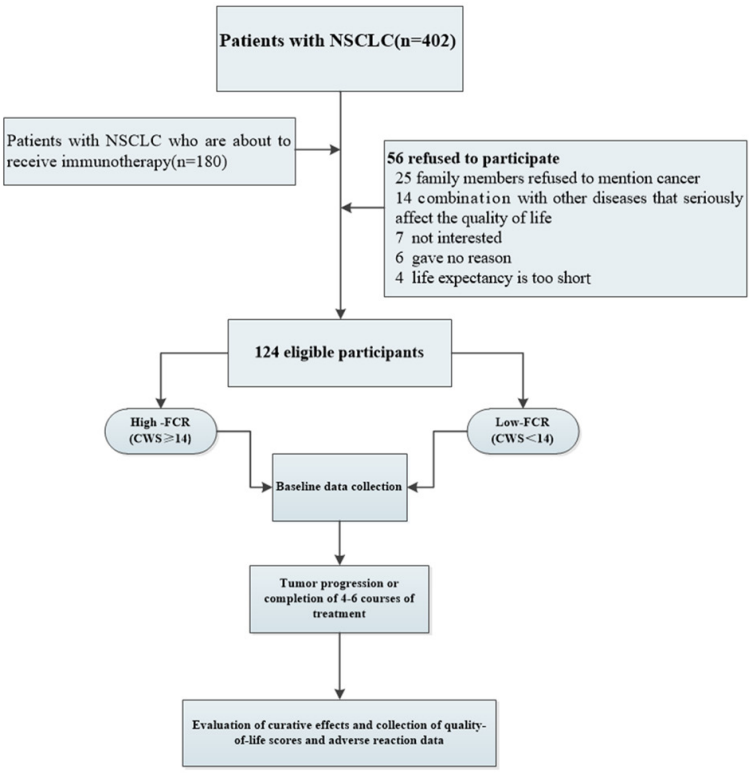

Figure 1. Research flowchart. Abbreviations: NSCLC, non-small cell lung cancer; FCR, fear of cancer recurrence.

size. An oncologist evaluated the treatment efficacy and collected all baseline demographic and clinical data, and a psychologist administered all questionnaires; both the oncologist and psychologist were blinded to other study details.

Measures

All questionnaires were completed with paper and pencil at baseline (time of enrollment, T0) and at the time of disease progression or after completion of 4-6 cycles of treatment (T1). Self-reported demographic and medical characteristics were collected at T0. Participants were screened for high FCR using the CWS, which measures concerns regarding cancer or a second cancer diagnosis. The CWS consists of eight items that are each scored from 1 (never) to 4 (almost always; α=.81), resulting in total overall scores ranging from 8 to 32. Lower CWS scores indicate lower FCR. The diagnostic cut-off values for distinguishing low FCR from high FCR in survivors of breast cancer and colorectal cancer were 13 and 14, respectively. In this study, patients with CWS scores ≥14 were classified as having high FCR [16].

Primary outcome

The Response Evaluation Criteria in Solid Tumors (RECIST) criteria were used to evaluate the efficacy of immunotherapy and calculate the disease control rate (DCR) and overall response rate (ORR). The RECIST criteria characterize the response of target lesions into four categories: (1) complete response (CR), in which all target lesions disappear; (2) partial response (PR), associated with a 30% reduction in the total length or diameter of baseline lesions; (3) stable disease (SD), in which the total length or diameter of baseline lesions decreases without reaching the PR value or increases without reaching the PD value; and (4) progressive disease (PD), associated with a 20% increase in the total length or diameter of baseline lesions or the detection of new lesions.

Secondary outcome

The Chinese version of the EORTC QLQ-C30 was used to assess the patient's quality of life. The Chinese version of the EORTC QLQ-C30 contains 30 items, including five functional scales (i.e., physical, role, emotional, cognitive, and social), nine symptom scales (i.e., fatigue, nausea and vomiting, pain, dyspnea, insomnia, loss of appetite, constipation, diarrhea, and financial difficulties), and a global health scale. The scores for each subscale were then converted to a score ranging from 0 to 100 according to the EORTC scoring manual guidelines. A higher score indicates more severe symptoms and worse quality of life [17].

Statistical analysis

All statistical analyses in this research were performed using version 26 of the Social Science Statistical Package (SPSS). The Kolmogorov-Smirnov test was used to verify

Table 1. Clinical characteristics of participants by study group

Characteristics	High-FCR				Low-FCR				t/X^2	P
	NO.	%	Mean	SD	No.	%	Mean	SD		
Age			63.82	9.785			62.28	10.239	-0.835	.405
Sex									0.131	.717
Male	48	64.8			34	68.0				
Female	26	35.2			16	32.0				
Education									1.892	.595
illiteracy	27	36.5			21	42.0				
primary school	22	29.7			16	32.0				
Middle school	15	20.3			10	20.0				
University and above	10	13.5			3	6.0				
KPS									2.381	.123
90	31	41.9			28	56.0				
80	43	58.1			22	44.0				
Tumor staging									1.918	.590
IV	61	82.4			36	72.0				
III	10	13.5			11	22.0				
II	2	2.7			2	4.0				
I	1	1.4			1	2.0				
Pathological type									1.168	.558
Adenocarcinoma	47	63.5			27	54.0				
Squamous cell carcinoma	24	32.4			20	40.0				
Others	3	4.1			3	6.0				
Treatment programs									2.217	.696
IT	8	10.8			5	10.0				
IT+CT	31	41.9			16	32.0				
IT+TT	25	33.9			20	40.0				
IT+CT+TT	6	8.1			7	14.0				
IT+others	4	5.4			2	4.0				
Immunotherapy drugs									.495	0.781
Camrelizumab	34	45.9			22	44.0				
Sintilimab	27	36.5			21	42.0				
Other	13	17.6			7	14.0				

Note: IT, Immunotherapy; CT, chemotherapy; TT, Targeted therapy; KPS, Karnofsky Performance Status.

whether the data conformed to a normal distribution. Baseline differences in demographic and medical characteristics between groups were independently analyzed by *t*-test or χ^2 analysis. Missing T1 values were imputed using a conservative approach in which the values were extrapolated from the most recent follow-up, as malignant tumors were expected to progress over time without intervention. We used the rank-sum test to compare differences in primary and secondary outcomes between the two groups, and linear regression was used to estimate the correlation between quality of life and FCR. All tests were two-tailed, and the significance level was set to 0.05.

Results

Participant characteristics

Table 1 shows the clinical characteristics of participants according to the study group. The study included 124 patients receiving immunotherapy for NSCLC. CWS scores were used to divide participants into the high-FCR group (n=74) and the low-FCR group (n=50). No significant differences in baseline characteristics

Table 2. Differences in efficacy between groups at the research endpoint

Efficacy	High-FCR	Low-FCR	Z	p
	No (%)	No (%)		
PR	6 (8.1)	16 (32.0)	-5.26	.000
SD	28 (37.8)	29 (58.0)		
PD	40 (54.1)	5 (10.0)		
ORR	6 (12.8)	16 (32.0)		
DCR	34 (45.9)	45 (90.0)		

Note: PR, partial response; SD, stable disease; PD, progressive disease; ORR, the objective response rate; DCR, disease control rate.

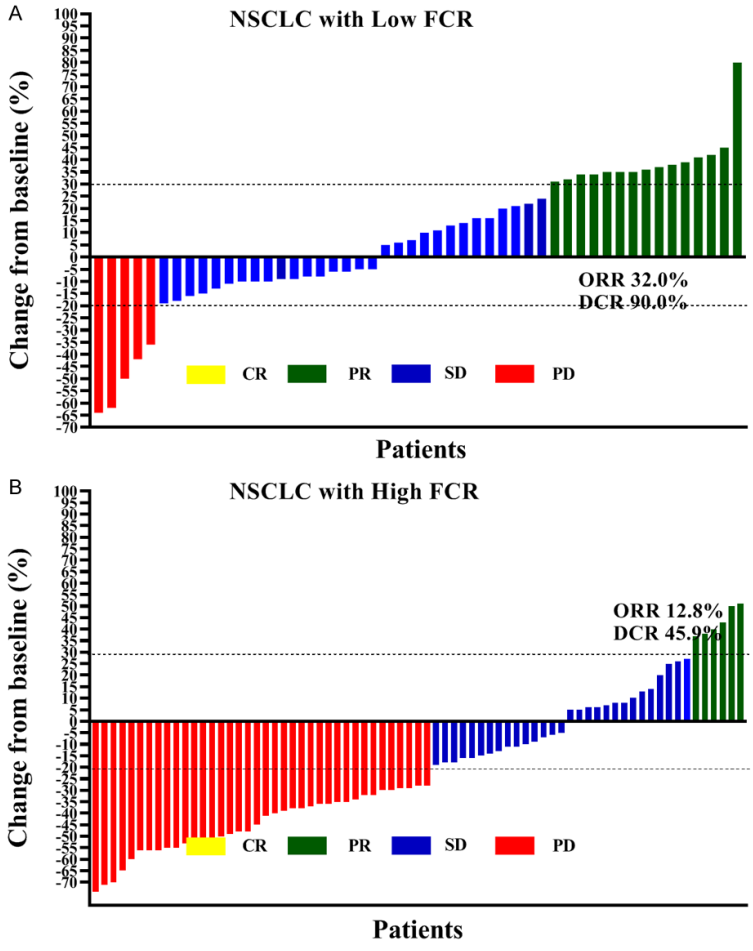

Figure 2. Differences in efficacy between groups at the research endpoint. A. Treatment efficacy and changes in the target lesions from baseline to the research endpoint for the low-fear of cancer recurrence (FCR) group. B. Treatment efficacy and changes in the target lesions from baseline to the research endpoint for the high-FCR group. NSCLC, non-small cell lung cancer; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, overall response rate; DCR, disease control rate.

were observed between groups, including age (63.82±9.785 years vs. 62.28±10.239 years, t=-0.835, P=0.405), sex (x^2=0.131, P=0.717), education level (x^2=1.892, P=0.595), pathological type (x^2=1.168, P=0.558), KPS (x^2=2.381, P=0.123), immunotherapy drugs (x^2=2.217, P=0.696), and tumor staging (x^2=1.918, P=0.590) (**Table 1**).

Primary outcome

Table 2 shows differences in efficacy at the research endpoint. In the high-FCR group, 6 patients had PR, 28 had SD, and 40 had PD, with the ORR reaching 12.8% and the DCR reaching 45.9%. In the low-FCR group, 16 people had PR, 29 had SD, and 5 had PD, with the ORR reaching 32% and DCR reaching 90%. A significant difference in the curative effect (Z=-5.26, P<.000) of immunotherapy was observed between groups (**Table 2**). Waterfall charts displaying the curative effects for both groups are shown in **Figure 2**.

Secondary outcome

Table 3 shows the EORTC QLQ-C30 scores at different time points. The EORTC QLQ-C30 scores for the high-FCR group ranged from 69±13.12 at baseline (T0) to 72.31±13.06 at the research endpoint (T1). The EORTC QLQ-C30 scores for the low-FCR group ranged from 5.08±12.63 at baseline (T0) to 59.54±12.14 at the research endpoint (T1) (**Table 3**). **Figure 3** shows the differences in EORTC QLQ-C30 scores at different time points. Both groups showed significant differences in EORTC QLQ-C30 scores between baseline (T0, z=-4.418, P=0.000) and the research endpoint (T1, z=-4.879, P=0.000). Compared with the baseline values, both the

Table 3. Differences in quality of life at different time point

QOL	High-FCR		Low-FCR		*Z*	*p*
	Mean	SD	Mean	SD		
T0	69.69	13.12	59.08	12.63	-4.148	.000
T1	72.31	13.06	59.54	12.14	-4.879	.000
T0-T1	-2.62	4.85	-0.46	4.73	-2.308	.021

Note: QOL, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; T0, The score of Qol-c30 at baseline; T1, The score of Qol-c30 at research endpoint; T0-T1, The change in QoL-c30 between the baseline and endpoint.

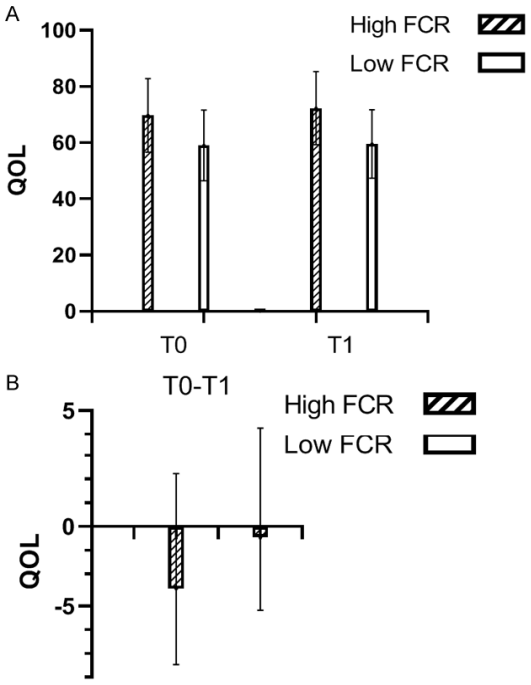

Figure 3. Differences in quality of life at different time points. A. Bar chart showing that the high-fear of cancer recurrence (FCR) group had higher QOL scores than the low-FCR group at both baseline (T0) and the research endpoint (T1). B. Bar chart comparing the change in QOL scores between baseline (T0) and the research endpoint (T1), showing a larger decline in QOL for the high-FCR group than for the low-FCR group. QOL: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30). T0-T1: Change in the EORTC QLQ-C30 score between baseline and the research endpoint.

high-FCR group (-2.62±4.85) and the low-FCR group (-0.46±4.73) showed a decrease in EORTC QLQ-C30 scores at the research endpoint. A significant difference in the amount of change was also observed between groups (z=-2.308, P=0.021, **Figure 3**). **Figure 4** shows the correlation between EORTC QLQ-C30 and CWS scores at different time points. The EORTC QLQ-C30 and the CWS scores were correlated at baseline (T0, R^2=0.398, P<0.000) and at the research endpoint (T1, R^2=0.484, P<0.000). The change in the EORTC QLQ-C30 score between baseline and the research endpoint also correlated with the CWS score (T0-T1, R^2=-0.264, P<0.05, **Figure 4**).

Adverse events

Table 4 shows the adverse reactions to immunotherapy. Both groups of advanced NSCLC patients had similar adverse events, with no significant differences in the occurrence of any event type. In the high-FCR group, we observed 14 patients with immune-related dermatitis, 1 with immune-related gastrointestinal reactions, 3 with immune-related pneumonia, and 2 with immune-related endocrine damage. In the low-FCR group, we observed 8 patients with immune-related dermatitis (x^2=0.174, P=0.676), 0 with immune-related gastrointestinal reactions (x^2=0.681, P=0.409), 1 with immune-related pneumonia (x^2=0.403, P=0.525), and 1 with immune-related endocrine damage (x^2=0.062, P=0.803).

Discussion

This study shows that FCR is a factor affecting quality of life and prognosis in patients with advanced NSCLC receiving immunotherapy. We discovered that the ORR and DCR of the high-FCR group were significantly lower than those of the low-FCR group. In addition, the participants with high FCR demonstrated a lower quality of life during treatment than those in the low-FCR group.

Tumor patients have been found to experience FCR, particularly patients with NSCLC. Past studies have commonly examined FCR risk factors and intervention measures [8-10, 18], but the impacts of FCR on tumor treatment have rarely been studied. Previous studies have examined the effects of negative psychological states and negative emotions, such as chronic stress [19-22], on the immune system in general patient populations, but few studies have described these psychological issues in pa-

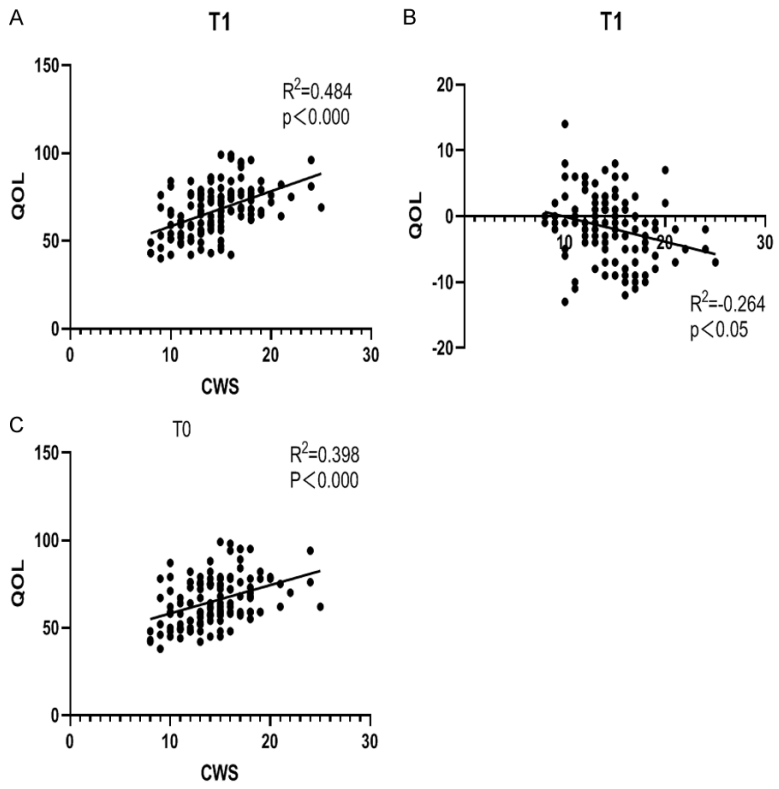

Figure 4. Correlation between the Cancer Worry Scale and quality of life at different time points. A. The EORTC QLQ-C30 score and the CWS score were correlated at baseline (T0, R^2=0.398, P<0.000). B. The change in the EORTC QLQ-C30 score between baseline and the research endpoint was also correlated with the CWS score at the research endpoint (T0-T1, R^2=-0.264, p<0.05). C. The EORTC QLQ-C30 score and the CWS score were correlated correlation at the research endpoint (T1, R^2=0.484, p<0.000). EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; CWS: the Cancer Worry Scale.

Table 4. Adverse reactions to immunotherapy

	High-FCR		Low-FCR		X^2	*p*
	No	%	No	%		
Immune-related dermatitis	14	18.9	8	16	*.174*	*.676*
Immune-related gastrointestinal reactions	1	1.4	0	0	.681	.409
Immune-related pneumonia	3	4.1	1	2.0	.403	.525
Immune-related endocrine damage	2	2.7	1	2.0	.062	.803

tients undergoing antitumor treatment, especially immunotherapy, from a clinical perspective.

Our study found that patients with high FCR tend to have poorer responses to immunotherapy. FCR is a fear emotion, and psychoneurological studies have suggested that the amygdala, a core region associated with fear physiology and behaviors [23], may increase the metabolic activity and activation of bone marrow, releasing inflammatory cells and leading to inflammation [24]. Chronic fear activates the sympathetic nervous system and the hypothalamic-pituitary-adrenal axis, which stimulates renin secretion and angiotensin II production, activating NADPH oxidase and leading to oxidative stress and the release of high concentrations of the stress hormone glucocorticoid [25]. High glucocorticoid concentrations suppress antigen-stimulated inflammation mediated by macrophages, dendritic cells, and epithelial cells and impair cytotoxic immune responses by downregulating interferon (IFN)-γ production and inhibiting the development of type-1 helper T cells, $CD8^+$ T cells, and natural killer cells [26]. In mice, Yang et al. observed that stress, elevated plasma corticosterone, and the upregulation of glucocorticoid-inducible factor Tsc22d3 blocked both type I IFN responses in dendritic cells and IFN-γ T cell activation. This process can subvert therapy-induced anticancer immunosurveillance [27]. Furthermore, Wiktorowska et al. observed that knockdown of the astrocytic glucocorticoid receptor in the central nucleus of the amygdala diminished conditioned fear expression and anxiety [28]. Therefore, we can assume that glucocorticoids may be an important factor in the mechanism through which FCR affects immunotherapy efficacy.

Specific changes in patient behavior are another explanation for the efficacy of immunotherapy. Lebel et al. pointed out that FCR includes five aspects: (1) high levels of pre-

occupation, worry, rumination, or intrusive thoughts; (2) maladaptive coping; (3) functional impairments; (4) excessive distress; and (5) difficulties making plans for the future. High FCR may aggravate patients' avoidance behaviors, which may manifest as delaying treatment times, exaggerating drug side effects, or changing treatment plans, and the resultant irregularity in treatment timing and the frequency of treatment adjustments may result in poor overall treatment efficacy.

Consistent with previous studies, patients' EORTC QLQ-C30 scores showed an inverse relationship with FCR [4, 18]. In this study, we observed that patients with stronger FCR experienced larger declines in EORTC QLQ-C30 scores. These results underscore the importance of continued research on FCR and highlight the need for interventions to alleviate FCR in patients.

There are some limitations of this research. First, this study was conducted as a single-center, small-sample study, and its findings may not be generalizable to patients at other centers. Second, this research did not simultaneously assess changes in FCR and quality of life among patients during follow-up. More follow-up questionnaire results may verify the study conclusions or help to explore the possible mechanisms. Finally, we did not follow participants long-term, and a longer follow-up period may provide us with more information regarding the impacts of FCR on immunotherapy efficacy in patients with NSCLC. The identification of biological indicators remains necessary to further explore the mechanisms through which FCR affects therapeutic outcomes, and our subsequent studies will address this gap.

During the COVID-19 pandemic, tumor treatment was disrupted to varying degrees [2, 29, 30], making FCR more prominent during this particular period [6]. Although more large-scale studies are needed to confirm this observation, this study has identified the potential impact of FCR on the efficacy of immunotherapy. This finding indicates that FCR is not only a psycho-oncological problem but also merits the attention of more clinical oncologists and other health professionals.

Conclusions

Our research confirms that FCR had significant impacts on immunotherapeutic efficacy and quality of life among patients with NSCLC during the COVID-19 pandemic. The findings of this research emphasize the need to pay close attention to the level of FCR experienced by NSCLC patients. Psychological interventions to alleviate FCR in patients with NSCLC are warranted. Future research should explore the possible internal link between immunotherapy and FCR.

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Disclosure of conflict of interest

None.

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