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# Associations of pretreatment emotional distress with adherence to therapy for patients with locally advanced rectal cancer: a post hoc analysis of the Chinese FOWARC phase 3 randomized clinical trial

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## Abstract

**Background** Non-adherence in advanced rectal cancer therapy is common and severely impairs clinical outcomes. Although behavioral research suggests emotional factors influence adherence, limited evidence links pretreatment emotional distress (PED) to treatment adherence in rectal cancer patients.

**Methods** This post hoc analysis of a phase 3 randomized clinical trial was conducted from June 9, 2010, to February 15, 2015, involving 219 patients (assigned to receive neoadjuvant therapy with fluorouracil plus radiotherapy [group A, 67 patients], modified fluorouracil, leucovorin, and oxaliplatin [mFOLFOX6] plus radiotherapy [group B, 66 patients], or mFOLFOX6 alone [group C, 86 patients] followed by TME resection and postoperative adjuvant chemotherapy) with locally advanced rectal cancer from the main center. The PED of patients was measured through the emotional dimension items in the Quality of Life Questionnaire-Core Questionnaire (QLQ-C30). The primary outcome was adherence to therapy, with non-adherence defined as patients in groups A and B receiving fewer than ten cycles of chemotherapy or less than 37 Gy of radiotherapy, and patients in group C receiving fewer than ten cycles of chemotherapy. Multivariable logistic regression models were used to estimate the odds ratios (ORs) and 95% confidence intervals (CIs) for adherence by PED levels. Additionally, the structural equation model (SEM) was utilized to analyze the impact pathways of PED on adherence.

**Results** Among the 219 patients (142 men; mean age, 53.4 years) who completed the QLQ-C30 scale, 27.8% (61/219) demonstrated non-adherence to the treatment regimen. Multivariable analyses showed that each 1-point increase in PED score raised non-adherence risk by 4.37 times (OR: 4.37, 95% CI: 1.92–9.96,  $P < 0.001$ ). The SEM analysis revealed that PED score was positively correlated with the risk of non-adherence (standardized regression coefficients [ $\beta$ ] = 0.25, 95% CI: 0.11 to 0.28), while economic burden was positively correlated with PED ( $\beta$  = 0.17, 95% CI: 0.11 to 0.28), and could indirectly affect adherence through PED ( $\beta$  = 0.04, 95% CI: 0.01 to 0.09).

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**Conclusions** Higher levels of pretreatment emotional distress were associated with an increased risk of treatment non-adherence, thereby highlighting the potential significance of addressing emotional distress in cancer management.

**Trial registration** ClinicalTrials.gov identifier: NCT01211210.

**Keywords** Treatment adherence, Rectal cancer, Emotional distress

## Background

Colorectal cancer, ranked as the third most prevalent cancer globally, remains one of the most common malignancies. Worldwide, an estimated 1.88 million new cases were diagnosed in 2020 [1]. Early-stage colorectal cancer is often asymptomatic, leading to delayed detection; approximately 60% of newly diagnosed cases are identified at advanced stages [2]. Furthermore, the proportion of rectal cancer among these new cases has increased from 27% in 1995 to 31% in 2019 [2].

Neoadjuvant chemoradiotherapy followed by total mesorectal excision (TME) is widely accepted as the standard of care for advanced rectal cancer. However, during this prolonged and complex treatment process, approximately 10 to 40% of patients may fail to adhere to the prescribed treatment plan [3–5]. These patients typically receive sub-standard doses of medication, resulting in therapeutic outcomes that fall short of expectations. Studies have shown that the 3-year recurrence risk for non-adherent patients is 1.8 times higher than that of patients who received full doses of treatment [6]. Despite this, the issue of non-adherence in rectal cancer treatment has not received sufficient attention, and research on relevant influencing factors remains limited.

As a negative behavior occurring during treatment, non-adherence among patients is believed to be closely related to emotional factors from the perspective of behavioral research, according to the Theory of Planned Behavior, which is widely used in the field of adherence research [7–9]. Patients experiencing emotional distress are more likely to become weary of long-term treatment and may develop resistance to continuing with the prescribed regimen; meanwhile, emotional distress can exacerbate the negative effects of early-stage treatment ineffectiveness or adverse reactions, leading to non-adherence [10, 11]. Previous studies focusing on chronic diseases that require long-term home medication, such as HIV/AIDS and tuberculosis, have found a close correlation between emotion and treatment adherence [12, 13], and relevant intervention measures have been developed to successfully improve adherence [13, 14]. However, there is a paucity of research on treatment adherence in the field of rectal cancer, with existing studies primarily examining the influence of the treatment regimen on patient adherence and neglecting the role of

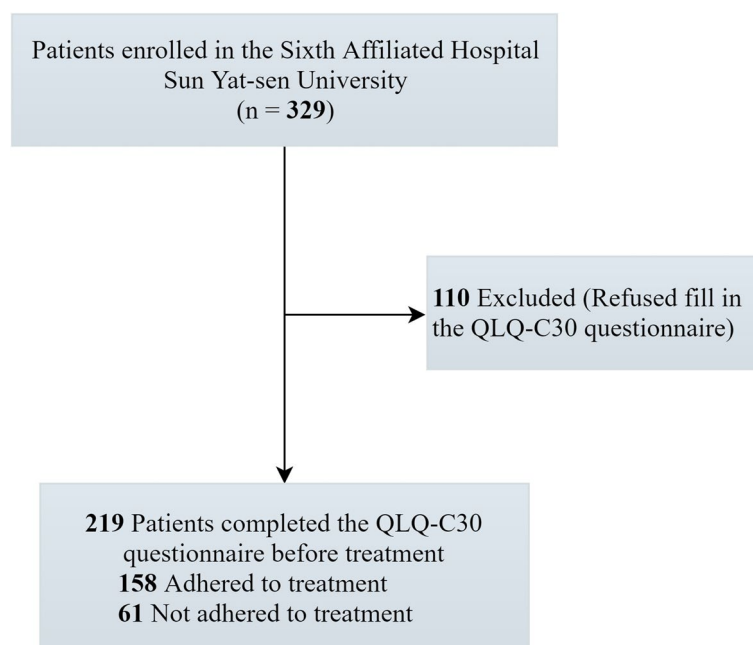
psychological factors [6, 15]. Given the substantial heterogeneity in adherence determinants across disease populations [16], coupled with the hospitalization-dependent treatment paradigm for rectal cancer patients (as contrasted with home-based therapeutic regimens prevalent in existing adherence literature), more evidence is needed to determine whether emotions are closely related to treatment adherence in rectal cancer patients. Meanwhile, considering the significant impact of adverse events and economic status on adherence in previous studies [7, 12–14], this study will further explore the joint association effect of adverse events, economic status, and emotions on adherence, which might be helpful to provide intervention strategies from a psychological perspective for these high-risk patients who may not adhere.

In summary, the current poor treatment adherence observed among patients undergoing advanced rectal cancer therapy has impaired clinical efficacy [6], yet clinical practice lacks corresponding strategies to address this issue [15]. This study, utilizing data from a high-quality prospective randomized controlled trial conducted in China, investigates the relationship between pretreatment emotional distress and treatment adherence, thereby offering a theoretical foundation for the future formulation of intervention strategies.

## Methods

### Study design and patients

The “FOWARC” trial (ClinicalTrials.gov identifier: NCT01211210) is an investigator-initiated, multicenter, phase III, three-arm randomized study, the details of which have been published previously [17, 18]. Participants in this study were recruited from patients who participated in the “FOWARC” trial at the main center (the Sixth Affiliated Hospital of Sun Yat-sen University) (Fig. 1). In brief, patients with stage II or III rectal adenocarcinoma were randomized to receive neoadjuvant fluorouracil (FU) plus radiotherapy (RT) (group A), mFOLFOX6 (modified fluorouracil, leucovorin, and oxaliplatin) chemotherapy plus radiotherapy (group B), or mFOLFOX6 alone (group C), before undergoing TME resection and adjuvant chemotherapy, during the period from 2010 to 2015. More detailed patient inclusion and exclusion criteria are available in the previously published literature [17, 18].



**Fig. 1** Formation of study cohort. Legends: QLQ-C30, Quality of Life Questionnaire-Core Questionnaire

Patients were enrolled by the study investigators (Yanhong Deng, Xiuping Deng, and Jianwei Zhang). After signing the informed consent at the inpatient department, the patients were advised to complete the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core Questionnaire (QLQ-C30) version 3.0 (paper-based) [19], and subsequently commenced treatment. Afterwards, the paper questionnaire was kept by Xiuping Deng in the office of the Clinical Research Center in the Sixth Affiliated Hospital, Sun Yat-sen University. The research process is shown in Additional file 1: Fig. S1. We adhered to the CONSORT statement in writing our paper (Additional file 2: CONSORT checklist).

## Procedures

### Radiotherapy

Patients who were randomly assigned to groups A and B received radiotherapy, which was administered at a dose of 1.8 to 2.0 Gy per day from Monday to Friday, for a total of 23 to 25 fractions over a period of 5 to 6 weeks, resulting in a total dose of 46.0 to 50.4 Gy.

### Chemotherapy

Patients who were randomly assigned to group A received preoperative treatment consisting of five cycles of fluorouracil, with concurrent radiotherapy administered during cycles 2 to 4, followed by postoperative chemotherapy with seven cycles of fluorouracil. Patients in group B

followed the same treatment regimen as those in the fluorouracil plus radiotherapy group, with the addition of oxaliplatin at a dose of 85 mg/m<sup>2</sup> intravenously on day 1 of each chemotherapy cycle. Patients assigned to group C received preoperative treatment with four to six cycles of mFOLFOX6 and postoperative chemotherapy with six to eight cycles of mFOLFOX6, with radiation administered either before or after surgery at the physicians' discretion. For more detailed information on the treatment regimens, please refer to the previously published literature [17, 18]. Thus, the complete treatment regime for all three groups included 12 chemotherapy cycles, including preoperative and postoperative chemotherapy cycles (see Additional file 1: Fig. S1).

## Independent variables

### Emotion

The pretreatment emotional state of patients was measured using the emotional dimension items from QLQ-C30. This emotional dimension comprised four items: "1. Did you feel tense? 2. Did you worry? 3. Did you feel irritable? 4. Did you feel depressed?". Each item offered four response options on a scale ranging from 1 ("Not at all") to 4 ("Very much"). The total emotional distress score was obtained by averaging the scores of these four items, with higher score indicating greater emotional distress. The QLQ-C30 scale is widely used in clinical trials related to tumors and has demonstrated good reliability and validity [20]. In this study, the Cronbach's alpha for

the four emotional items was 0.67, consistent with previous study [19].

### Demographic and other covariates

To better understand the association between emotion and treatment adherence among patients with locally advanced rectal cancer, factors that might be associated with treatment adherence were also included in the analysis as covariates [16, 21–23].

The demographic variables included in the analysis were economic status (categorized as good or poor), which was measured through the 28th item of the QLQ-C30, asking “Has your physical condition or medical treatment caused you financial difficulties?” on a scale ranging from 1 (“Not at all”) to 4 (“Very much”), with score of 1–2 indicating a good economic condition and score of 3–4 indicating a poor economic condition; sex (male or female); and age (categorized as either <60 or ≥60 years).

The clinical characteristic variables included in the analysis were treatment regimen (categorized as FU+RT, mFOLFOX6+RT, or mFOLFOX6); clinical T (cT) category (cT2–3 or cT4); clinical N (cN) category (cN0 or cN1–2); tumor length (≥4 cm or <4 cm); and distance from the anal verge (≥5 cm or <5 cm). Detailed measurement and judgment methods for these indicators can be found in the previously published literature [17].

The adverse events included in the analysis were anastomotic leakage (yes or no), defined as communication between the intra- and extra-luminal compartments; adverse reactions to chemotherapy (yes or no), defined as grade 3–4 leukopenia, neutropenia, or hemoglobinopenia; and adverse reactions to radiotherapy (yes or no), defined as grade 3–4 radiation enteritis or perianal inflammation. Acute adverse events that occurred during or within 30 days after chemoradiotherapy or adjuvant chemotherapy were graded according to the Common Terminology Criteria for Adverse Events (version 3).

### Outcomes

The main outcome in this study was adherence to therapy for patients with locally advanced rectal cancer. Based on the results of previous studies [6, 15], adherence to therapy was defined as receiving at least 80% of the prescribed courses and doses of radiotherapy. Therefore, in this study, patients who received fewer than ten cycles of chemotherapy (including preoperative and postoperative) or less than 37 Gy of radiotherapy in groups A and B, and who received fewer than ten cycles of chemotherapy (including preoperative and postoperative) in group C, were defined as non-adherent.

### Statistics

Baseline characteristics were presented as *n* (%) for categorical variables, mean (SD) for normally distributed continuous variables, and median (IQR) for non-normally distributed continuous variables. Differences among groups were assessed using ANOVA and  $\chi^2$  tests, with the Kruskal–Wallis test employed for non-normally distributed data. No imputation for missing data was necessary, as patients who did not complete the QLQ-C30 questionnaire at baseline were directly excluded from the analysis.

Multivariable logistic regression models were employed to estimate the odds ratio (OR) and 95% confidence intervals (CIs) for treatment adherence (0: adherence; 1: non-adherence) associated with emotional distress, while adjusting for various covariates. Three models were constructed: in model 1, adjustments were made for economy (0: good; 1: poor), age (0: <60; 1: ≥60), sex (0: male; 1: female), and treatment regimen (0: FU+RT; 1: mFOLFOX6+RT; 2: mFOLFOX6); in model 2, the variables in model 1 were adjusted in addition to clinical T category (cT) (0: cT2–3; 1: cT4), clinical N category (cN) (0: cN0; 1: cN1–2), tumor length (0: <4 cm; 1: ≥4 cm), and distance from the anal verge (0: <5 cm; 1: ≥5 cm); and in model 3, further adjustments were made to include anastomotic leakage (0: no; 1: yes) and adverse reactions to chemotherapy (0: no; 1: yes).

A joint association analysis was also conducted to assess the relationship between emotional distress and treatment adherence, stratified by economic status and adverse events. To increase statistical power [24], adverse events were grouped into two categories: patients without any adverse reactions (no) and those with any adverse reactions (yes). To quantify the multiplicative interactions, product terms of emotion (continuous) and economy (good or poor), as well as product terms of emotion (continuous) and adverse events (no or yes), were included in the model. Adverse events or economic status were included as moderator in the analysis, while all other covariates were included as confounding factors. The *P* value of the product term served as the measure of interaction on the multiplicative scale.

With the aim of formulating behavioral intervention strategies, a structural equation model (SEM) was constructed, a technique widely used in the field of behavioral health studies [25, 26], to explore the behavioral mechanisms through which pretreatment emotion influences adherence. Initially, a theoretical framework for the model was developed, drawing from prior literature [16, 21–23], positing that demographic factors and baseline clinical characteristics could influence adherence both by impacting emotion and directly; while the treatment regimen, not affected by other factors due to the random

allocation of patients, may directly affect adherence; and adverse events arising during the treatment process may be influenced by the treatment plan and may also directly impact adherence. The theoretical model, based on the aforementioned assumptions, is presented in Additional file 1: Fig. S2. Subsequently, the maximum likelihood method was used to construct the SEM, and data-model fitting in the SEM analysis was assessed using the following indices: goodness of fit index (GFI) ( $>0.9$ ), comparative fit index (CFI) ( $>0.9$ ), root mean square error of approximation (RMSEA) ( $<0.05$ ), and the chi-square associated with each degree of freedom (CMIN/df) ( $<3$ ). All reported  $\beta$  values are presented as standardized regression coefficients.

Several sensitivity analyses were conducted to ensure the robustness of the findings. First, a dichotomized emotional distress score ( $<1.5$  or  $\geq 1.5$ ) was created to account for the associations between emotional distress and treatment adherence. Second, to address the controversy surrounding treatment adherence standards, the definition of non-adherence was adjusted to when a patient completed less than 70% of the prescribed courses ( $<9$  cycles of chemotherapy) or doses of radiotherapy ( $<33$  Gy). Third, patients in group C, who did not undergo radiotherapy, were excluded, and logistic regression analysis was conducted solely on groups A and B patients, with additional adjustments made for adverse reactions to radiotherapy. All analyses were performed using R statistical software version 4.3.0 (R Foundation), with two-sided  $P$  values  $<0.05$  considered significant.

#### Role of the funding source

The funders were not involved in the study design, data collection, data analysis, interpretation, or writing of the report. All authors have reviewed and approved the final manuscript and share responsibility for the decision to submit it for publication.

#### Results

A total of 329 patients were enrolled at the Sixth Affiliated Hospital of Sun Yat-sen University. After excluding 110 patients who did not complete the QLQ-C30 questionnaire at baseline, 219 patients were included in the final analyses (see Fig. 1). No statistically significant differences were observed in clinical characteristics and treatment adherence between participants and non-participants (Additional file 1: Table S1). Among the 219 patients, 61 experienced non-adherence to the treatment plans, resulting in a non-adherence rate of 27.8%, with 26.9% (59/219) having fewer than 10 chemotherapy cycles and 7.5% (10/133) receiving less than 37 Gy of radiotherapy. Patients who did not adhere to the treatment plan had significantly higher baseline emotional

distress score compared to those who adhered, and patients with a distance from the anal verge of less than 5 cm also exhibited higher non-adherence rates. Other factors, such as treatment regimen, economic status, and the incidence of adverse events, did not significantly differ between patients who adhered to the treatment plan and those who did not, as shown in Table 1.

The results of the multivariable logistic regression indicated a strong correlation between pretreatment emotional distress and treatment adherence, with stability maintained despite the gradual inclusion of confounding variables. As shown in Table 2, the final model (model 3) revealed that for every one-point increase in the emotional distress score of patients, the risk of non-adherence to the treatment increased by 4.37 times (OR: 4.37, 95% CI: 1.92 to 9.96,  $P<0.001$ ).

No significant multiplicative interactions were found between emotion and economic status or adverse events on the incidence of non-adherence. Regardless of whether patients faced economic challenges or experienced adverse events during treatment, pretreatment emotional distress score was positively correlated with the risk of non-adherence, with no significant change in the effect size ( $P$ -interaction = 0.684 and 0.365, respectively), as shown in Table 3.

The outcomes of the SEM further corroborated those of the multivariable logistic regression, demonstrating a strong correlation between baseline emotional distress score and treatment adherence, with poorer emotional states significantly increasing the likelihood of non-adherence ( $\beta=0.25$ , 95% CI: 0.11 to 0.28). Additionally, a poorer economic status was associated with more negative emotional states ( $\beta=0.17$ , 95% CI: 0.11 to 0.28), and economic difficulties could also indirectly influence adherence through their impact on emotional distress ( $\beta=0.04$ , 95% CI: 0.01 to 0.09). It was also found that patients with tumors located less than 5 cm from the anal margin were more susceptible to non-adherence ( $\beta=-0.17$ , 95% CI:  $-0.29$  to  $-0.05$ ). The direct and indirect effects of these factors on adherence are depicted in Fig. 2 and Additional file 1: Table S2. The data-model fit indices for the SEM demonstrated excellent performance across all metrics, with GFI = 0.967, CFI = 0.981, RMSEA = 0.018, CMIN/df = 1.07, and  $P=0.361$ , attesting to the reliability of the identified impact pathways.

The results of the sensitivity analysis further support the correlation between pretreatment emotional states and treatment adherence. After dichotomizing the emotional distress score, it was observed that patients with an emotional distress score above 1.5 had a significantly higher risk of non-adherence to treatment compared to those with a score of 1.5 or below (OR = 4.91; 95% CI: 2.43 to 9.93;  $P<0.001$ ). Even after adjusting the definition



**Table 1** Characteristics of patients adhered and non-adhered to treatment

Variables	Total (n=219)	Adhered (n=158)	Non-adhered (n=61)	P value
Emotion, mean $\pm$ SD	1.34 $\pm$ 0.41	1.27 $\pm$ 0.39	1.50 $\pm$ 0.41	< 0.001
Economy, n (%)				0.493
Good	165 (75.34)	121 (76.58)	44 (72.13)	
Poor	54 (24.66)	37 (23.42)	17 (27.87)	
Sex, n (%)				0.16
Male	142 (64.84)	98 (62.03)	44 (72.13)	
Female	77 (35.16)	60 (37.97)	17 (27.87)	
Age, n (%)				0.658
< 60	145 (66.21)	106 (67.09)	39 (63.93)	
$\geq$ 60	74 (33.79)	52 (32.91)	22 (36.07)	
Treatment regime, n (%)				0.116
FU + RT	67 (30.59)	43 (27.22)	24 (39.34)	
mFOLFOX6 + RT	66 (30.14)	53 (33.54)	13 (21.31)	
mFOLFOX6	86 (39.27)	62 (39.24)	24 (39.34)	
cT category, n (%)				0.779
cT2–3	175 (79.91)	127 (80.38)	48 (78.69)	
cT4	44 (20.09)	31 (19.62)	13 (21.31)	
cN category, n (%)				0.739
cN0	50 (22.83)	37 (23.42)	13 (21.31)	
cN1–2	169 (77.17)	121 (76.58)	48 (78.69)	
Tumor length, n (%)				0.067
< 4 cm	108 (49.32)	84 (53.16)	24 (39.34)	
$\geq$ 4 cm	111 (50.68)	74 (46.84)	37 (60.66)	
Distance from anal verge, n (%)				0.008
< 5 cm	84 (38.36)	52 (32.91)	32 (52.46)	
$\geq$ 5 cm	135 (61.64)	106 (67.09)	29 (47.54)	
Anastomotic leakage, n (%)				0.667
No	202 (92.24)	147 (93.04)	55 (90.16)	
Yes	17 (7.76)	11 (6.96)	6 (9.84)	
Adverse reactions to chemotherapy, n (%)				0.065
No	160 (73.06)	110 (69.62)	50 (81.97)	
Yes	59 (26.94)	48 (30.38)	11 (18.03)	

mFOLFOX6, modified fluorouracil, leucovorin, and oxaliplatin, FU fluorouracil, RT radiotherapy, SD standard deviation, cT clinical T, cN clinical N

of adherence, the association between emotional distress and adherence remained strong (OR = 2.89; 95% CI: 1.14 to 7.29;  $P = 0.025$ ). When considering only individuals who underwent radiation therapy ( $N = 133$ ) and additionally controlling for adverse events, worse emotional states were still associated with a higher rate of non-adherence (OR = 2.55; 95% CI: 0.87 to 7.42;  $P = 0.086$ ), potentially due to the reduced sample size, which might have led to the non-significance of the association.

## Discussion

Non-adherence to treatment during rectal cancer therapy can significantly impair clinical efficacy, making it a critical clinical issue. To our knowledge, this is the first study

in China to utilize data from a high-quality clinical trial to explore the association between pretreatment emotional distress and treatment adherence in rectal cancer patients. Unlike previous studies that primarily focused on the influence of drug selection or dosing on patient adherence within rectal cancer treatment regimes [6, 15, 27], this study investigated the psychological factors influencing patient adherence from a behavioral perspective. It found a strong correlation between pretreatment emotional distress and treatment adherence in rectal cancer patients, thereby offering a theoretical foundation for formulating effective adherence intervention strategies in the future, while preserving the stability of the treatment regimen.

**Table 2** Associations between pretreatment emotion and treatment adherence after the adjustment of covariates

Variables	Model 1		Model 2		Model 3	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Emotion	4.33 (1.99 to 9.42)	< 0.001	4.24 (1.90 to 9.49)	< 0.001	4.37 (1.92 to 9.96)	< 0.001
Economy						
Good (ref)	1		1		1	
Poor	0.90 (0.43 to 1.87)	0.773	0.86 (0.40 to 1.85)	0.706	0.92 (0.42 to 2.00)	0.834
Sex						
Male (ref)	1		1		1	
Female	0.55 (0.28 to 1.10)	0.089	0.53 (0.26 to 1.09)	0.084	0.59 (0.28 to 1.22)	0.151
Age						
< 60 (ref)	1		1		1	
≥ 60	1.33 (0.68 to 2.59)	0.409	1.21 (0.60 to 2.43)	0.591	1.33 (0.65 to 2.71)	0.440
Treatment regime						
FU + RT (ref)	1		1		1	
mFOLFOX6 + RT	0.43 (0.18 to 0.98)	0.044	0.45 (0.19 to 1.05)	0.064	0.50 (0.21 to 1.22)	0.127
mFOLFOX6	0.75 (0.36 to 1.54)	0.431	0.86 (0.40 to 1.83)	0.694	0.94 (0.44 to 2.04)	0.883

Model 2 additionally adjusted for cT category, cN category, tumor length, and distance from anal verge based on model 1; model 3 additionally adjusted for anastomotic leakage and adverse reactions to chemotherapy based on model 2; mFOLFOX6, modified fluorouracil, leucovorin, and oxaliplatin, FU fluorouracil, RT radiotherapy, OR odd ratios, CI confidence interval

**Table 3** The relationship between emotional distress score and treatment adherence, stratified by economic status and adverse events

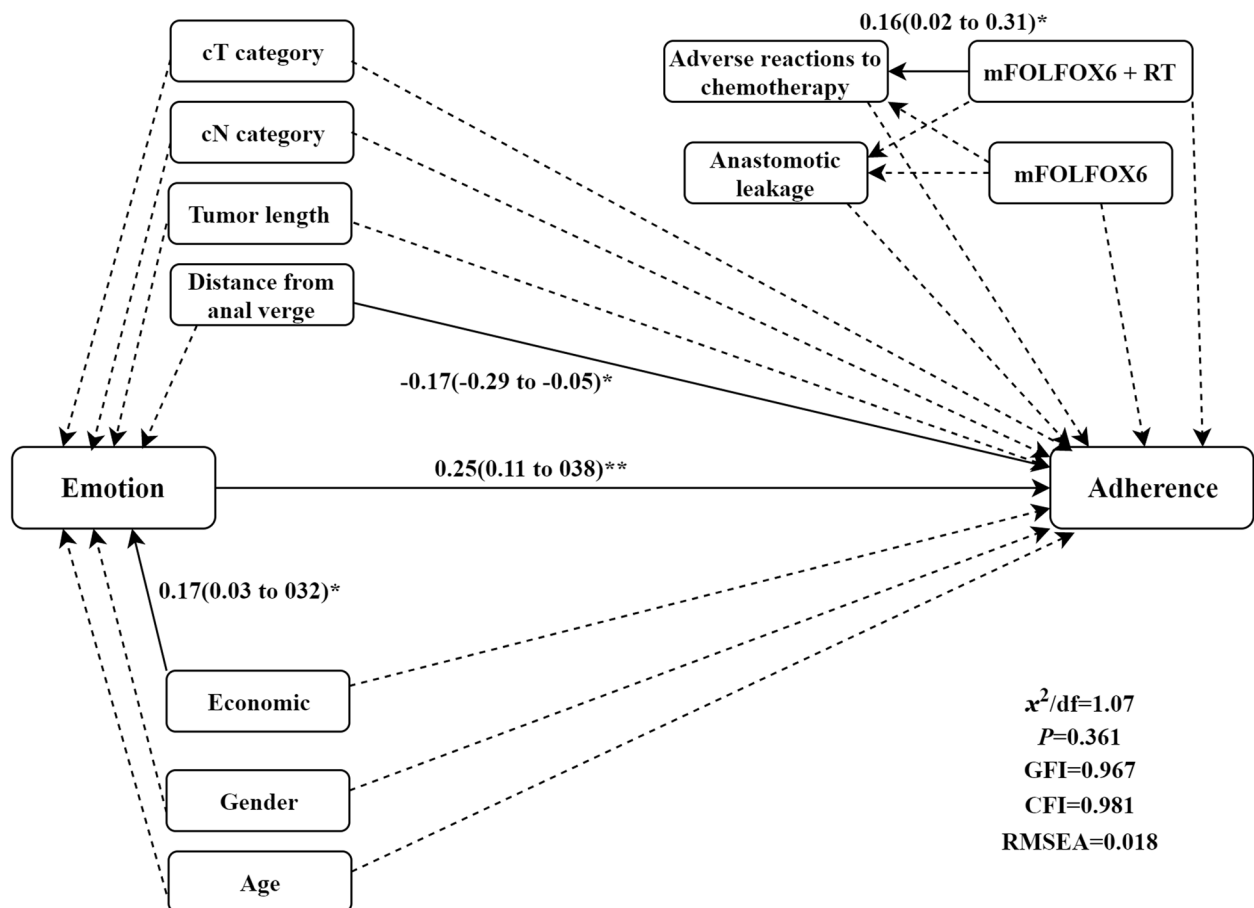
Subgroups	OR (95% CI)*	P value	P <sub>interaction</sub>
Economy			0.684
Good	5.18 (2.29 to 11.69)	< 0.001	
Poor	4.30 (0.90 to 20.52)	0.067	
Adverse events			0.365
No	4.98 (1.79 to 13.87)	0.002	
Yes	5.06 (0.76 to 33.48)	0.093	

\*adjusted for all covariates other than stratified variable; OR odd ratios, CI confidence interval

The rate of treatment non-adherence in rectal cancer patients is approximately 27.8%, which is comparable with previous studies [7, 16, 28]. The majority of non-adherence was reflected in the reduction of chemotherapy cycles. The results of logistic regression indicated that pretreatment emotional distress was associated with treatment non-adherence. While the association between emotions and adherence has been frequently observed in other chronic diseases requiring long-term medication [12, 13], this is the first time that such an association has been found in patients undergoing rectal cancer treatment. Although hospitalization has reduced the impact of forgetting on treatment adherence [16, 21], rectal cancer patients do not exhibit better adherence than those with chronic illnesses in previous studies [29, 30]. Previous research has demonstrated the influence of emotions

on the efficacy of therapy in cancer patients [31–33]. This study underscored the significance of emotional management in rectal cancer treatment by highlighting the crucial role of emotional factors in adherence.

This study also seeks to elucidate the mechanisms by which emotions influence adherence, such as whether patients with pretreatment emotional distress are more inclined to abandon standardized treatment due to economic burden or adverse events. The results did not identify any joint effects among these factors in their impact on patients' treatment adherence. On one hand, the limited sample size may have resulted in insufficient power to detect interactive effects [34]; on the other hand, as a nationally renowned tertiary hospital specializing in digestive diseases, the Sixth Affiliated Hospital of Sun Yat-sen University charges higher treatment fees than primary healthcare institutions and attracts a lot of inter-regional patients demonstrating stronger financial capacity for anticipated treatment costs [35]. Consequently, cost-sensitive populations may self-select out of seeking care at this institution, resulting in their underrepresentation within the study cohort. This could also explain why the logistic regression failed to demonstrate a correlation between economic factors and adherence, as well as why economic status did not show a joint effect with pretreatment emotions on adherence in this study. Meanwhile, it is noteworthy that the relationship between economic status and adherence remains controversial in previous literature [36]. Our study corroborated this complexity: while no direct association was observed between



**Fig. 2** Structural equation modeling of pretreatment emotion, demographic variables, clinical characteristics, and treatment adherence. Legends: Standardized path coefficients and corresponding 95% confidence intervals were reported, and dotted line represents non-significant paths; \* $P < 0.05$ , \*\* $P < 0.01$ ; GFI, goodness of fit index; CFI, confirmatory fit index; RMSEA, root mean square error of approximation;  $\chi^2/df$ , chi-square associated with each degree of freedom; mFOLFOX6, modified fluorouracil, leucovorin, and oxaliplatin; RT, radiotherapy

economic status and adherence, the SEM analysis further demonstrated that economic status was closely linked to pretreatment emotions and could exert an indirect effect on adherence via pretreatment emotions. These findings further underscored the significant role of pretreatment emotions in adherence research among rectal cancer patients. Subsequent multicenter observational studies with large sample sizes are warranted to further explore the economy-emotion interplay and its association with treatment adherence in these patients.

Regarding adverse events, many studies have identified them as important influencing factors in treatment adherence among patients with chronic diseases [16, 23]. However, in research related to cancer treatment, it is not uncommon to find that adverse events are not related to adherence [15, 27], which is consistent with the results of this study. This discrepancy might be due to the fact that, compared to patients receiving medication at home, adverse events in hospitalized patients

are addressed promptly. Additionally, it is important to note that these results are derived from clinical trials, where patients receive dedicated care and timely, thoughtful services to address adverse events [37]. Whether the adverse reactions caused by the treatment of rectal cancer patients have an impact on their adherence in routine care settings remains a topic for further exploration.

The SEM analysis also suggested that patients whose tumors were clinically confirmed with a distal border located less than 5 cm from the anal verge exhibited poorer adherence compared to those with tumors located more than 5 cm from the anal verge. This may be due to the fact that patients with lesions closer to the anal verge suffer more damage to anal function after radiotherapy, significantly affecting their quality of life and leading to the abandonment of subsequent chemotherapy treatment [38]. Consequently, more attention should be paid



to preserving anal function to enhance adherence during the treatment of rectal cancer patients.

Finally, considering the potential impact of the relatively subjective definition for treatment adherence in rectal cancer patients on the findings, we performed sensitivity analysis after adjusting the definition of adherence. As the adherence determination threshold varied between 70 and 80%, the association between emotional status and adherence remained stable, demonstrating the reliability of our findings. Future large-scale cohort studies may be necessary to provide more data support for defining treatment adherence in rectal cancer patients.

### Limitation

This study has several limitations. Firstly, the scope of participants was limited, consisting solely of patients from the main center who generally exhibited a strong willingness to receive treatment. Secondly, the clinical trial may not be the optimal study design to measure therapy adherence. Patients enrolled in clinical trials received dedicated care and timely services [37], interventions that could not be replicated in actual clinical settings, potentially leading to improved adherence to treatment regimens. Thus, both of these factors may result in adherence rates and the effect size between emotion and adherence found in this trial study differing from those observed in routine care for rectal cancer patients, and large-scale observational study are warranted in the future to validate the findings. Thirdly, previous adherence-related studies have also focused on factors such as family support, trust in doctors, and education level [16, 21], but these variables could not be adjusted for in this study due to their unavailability. Fourthly, this research only examined the relationship between pretreatment emotion and adherence; therefore, future longitudinal studies are needed to investigate the relationship between dynamic changes in patient emotions during treatment and adherence. Lastly, due to small sample size, the SEM analysis may not be able to identify all potential pathways that affect adherence, and larger sample studies are needed to obtain more reliable conclusions in the future.

### Conclusions

Our study revealed that higher levels of pretreatment emotional distress are associated with an increased risk of treatment non-adherence during advanced rectal cancer therapy, and this association was relatively stable and not found affected by the patient's economic status or adverse events during treatment. Meanwhile, economic status indirectly affected adherence through emotion, implying that pretreatment emotional

distress may also play an important role in the pathways through which other factors affect adherence. These findings indicated psychological intervention to rectal cancer patients may be a potential strategy to improve treatment adherence, and highlighted the significance of addressing emotional distress in rectal cancer management.

### Abbreviations

PED	Pretreatment emotional distress
CI	Confidence interval
QLQ-C30	Quality of Life Questionnaire-Core Questionnaire
OR	Odds ratio
SEM	Structural equation model
TME	Total mesorectal excision
mFOLFOX6	Modified fluorouracil, leucovorin, and oxaliplatin
FU	Fluorouracil
RT	Radiotherapy
cT	Clinical T category
cN	Clinical N category
EORTC	European Organisation for Research and Treatment of Cancer
GFI	Goodness of fit index
CFI	Comparative fit index
RMSEA	Root mean square error of approximation
CMIN/df	Chi-square associated with each degree of freedom

### Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s12916-025-04128-5>.

Additional file 1: Fig. S1 Study design. Fig. S2 Theoretical model framework of emotional distress influence on treatment adherence in patients with rectal cancer. Table S1 Characteristics of patients filled and not filled in the QLQ-C30. Table S2 Effects of emotion, economy, and distance from anal verge on treatment adherence.

Additional file 2: CONSORT checklist.

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### Authors' contribution

L.S. was involved in the study design, data analysis and interpretation of the results, and drafting the manuscript. J.Z. was involved in data collection, interpretation of the results and revision of the manuscript. Y.D. was involved in conception of the study, study design, data collection, interpretation of the results. All authors read and approved the final manuscript.

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### Data availability

Data are not publicly available due to their containing information that could compromise the privacy of research participants. Summary data can be made available from the corresponding author on reasonable request.

## Declarations

### Ethics approval and consent to participate

Written informed consent was obtained from all participants, and the study received approval from the Medical Ethics Committee of the Sixth Affiliated Hospital, Sun Yat-sen University (No. 2010017).

### Consent for publication

Not applicable.

### Competing interests

The authors declare no competing interests.

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