Supportive Care in Cancer (2023) 31:669
https://doi.org/10.1007/s00520-023-08143-1

RESEARCH

Psychological distress as a risk factor for the efficacy of chemotherapy in advanced gastric cancer patients

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Received: 3 February 2023 / Accepted: 24 October 2023 / Published online: 3 November 2023

Abstract

Aim To assess the relationship between psychological distress and quality of life (QoL), cancer-related fatigue (CRF), and chemotherapy efficacy in advanced gastric cancer patients.

Methods Advanced gastric cancer patients (39 with psychological distress and 35 without psychological distress) completed the Distress Thermometer (DT), QoL, and CRF test before receiving chemotherapy and assessed the efficacy after completing 2 courses of chemotherapy.

Results Psychological distress was a significant factor in the efficacy of chemotherapy in advanced gastric cancer patients ($\chi^2 = 6.324$; $p = 0.042$). Compared to advanced gastric cancer patients with no psychological distress, advanced gastric cancer patients with psychological distress had a poorer QoL (50.41 ± 6.17 vs. 60.01 ± 7.94, $t = -5.882$, $p < 0.01$) and more pronounced CRF (5.75 ± 1.16 vs. 3.22 ± 0.75, $t = 11.231$, $p < 0.01$) while receiving chemotherapy. FACT-G ($p = 0.0035$, $r = -0.4568$), as well as PFS ($p < 0.0001$, $r = 0.6599$), correlated significantly with efficacy for patients in the psychological distress group. The FACT-G ($p = 0.0134$, $r = -0.4139$) of patients in the no psychological distress group correlated significantly with efficacy.

Conclusion Psychological distress has a negative impact on QoL, CRF, and efficacy and may be a potential risk for the efficacy of palliative chemotherapy in advanced gastric cancer patients.

Keywords Advanced patients · Gastric cancer · Psychological distress · Cancer-related fatigue · Quality of life · Chemotherapy

Introduction

Gastric cancer (GC) is the fifth most common cancer worldwide and the absolute number of cases has remained stable or even increased due to the increase in the world's population and life expectancy [1]. There is therefore an interest in the QoL and prognosis of GC survivors. Psychological distress has been defined as "a multifactorial unpleasant emotional experience of a psychological, social, and/or spiritual nature that may interfere with the ability to cope effectively with cancer, its physical symptoms, and its treatment" [2]. The International Society of Psychological Oncology has classified psychological distress as the sixth vital sign, with up to 30% of GC patients experiencing psychological distress [3]. Most GC patients face varying degrees of psychological distress from the time the disease is first diagnosed until it progresses beyond cure and is associated with worse outcomes [4]. Studies have shown that 70.6% of advanced cancer patients exhibit high levels of psychological distress, significantly higher than those with early-stage cancer [5]. Therefore, the importance of psychological distress in advanced GC patients for the decision of treatment will continue to grow.

QoL is quite a subjective concept, which is accepted as a subjective multidimensional concept aiming to function satisfactorily in four core domains (physical, psychological, social, and functional well-being) [6, 7]. Several attempts

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have been made in the past to give a precise definition of QoL, but no consensus has been reached [8]. Accepting this impossibility, a practical solution is to describe the four main health dimensions of QoL mentioned above [9]. In order to have a comprehensive understanding of QoL in GC patients, taking into account the disease characteristics, treatment side effects, and emotional issues specific to gastric cancer, the main scales applicable to assessing QoL in gastric cancer patients are the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30, and the Functional Assessment of Cancer Therapy-General (FACT-G). Previous studies have shown a negative association between both physical and psychological symptoms and QoL in cancer patients [10]. Studies based on breast cancer have found that psychological distress is associated with a reduction in health-related QoL [11]. And a review of patients with advanced genitourinary cancers found that the great psychological distress faced by patients can lead to impaired QoL [12]. Gastric cancer itself, as well as various treatment modalities, may affect a patient's QoL. Among the psychological domains that affect QOL, psychological distress appears to have a greater impact [13]. It is important to study the factors that affect QoL so that clinicians can identify patients who may be more susceptible to these conditions and manage them appropriately for more effective remission and increased QOL. CRF is defined as "a distressing, persistent, subjective feeling of fatigue or exhaustion associated with cancer or cancer treatment that is out of proportion to recent activity and significantly interferes with normal function" [14]. CRF is multifaceted and may have physical and emotional manifestations, including general weakness, decreased concentration, reduced motivation or interest in engaging in daily activities, and emotional instability [15]. During palliative care, CRF is one of the most common symptoms of advanced cancer. As CRF is difficult to relieve with basic rest or sleep, it often affects the patient's QoL, and in severe cases, even the patient's compliance with treatment or the regularity of the course of treatment, thus affecting the outcome.

With improvements in the treatment room approach, chemotherapy-based systemic therapy has improved the survival of advanced GC patients [16, 17]. Identifying the risk factors that influence the efficacy of chemotherapy in advanced GC patients remains one of the current research priorities. However, clarifying the impact of patients' psychological distress on CRF, QoL, and even therapeutic effectiveness is equally important to clarify and improve patient prognosis. Especially for patients with advanced gastric cancer who may have more psychological distress, understanding the impact of psychological distress on therapeutic effectiveness in the palliative chemotherapy state may be one way to improve therapeutic effectiveness as well as survival. This study aimed to find out whether the level of psychological distress in patients with stage 4 gastric cancer in palliative chemotherapy correlates with CRF, QoL, and efficacy.

Materials and methods

Test design

This cohort study explored the effects of psychological distress on chemotherapy efficacy, CRF, and QoL among advanced stomach cancer patients receiving palliative chemotherapy. We collected baseline data from all participants at the time of study enrollment, including metastases tumor size, distress thermometer (DT), FACT-G, and Piper Fatigue Scale (PFS). Patients scoring ≥ 4 points on the DT were classified as having distress, whereas patients scoring ≤ 3 points were classified as having no distress [18]. Evaluation of efficacy after completion of 2 courses of dividend chemotherapy. This research was approved by the Research Ethics Committee of the Second Affiliated Hospital of Anhui Medical University (Number of Ethical Approval: 2,012,088). All participants provided oral informed consent to participate in this study.

Participants

All patients are selected according to the following criteria: (1) pathologically confirmed stage 4 gastric cancer with a target lesion for which efficacy can be assessed; (2) patients with a Karnofsky Performance Status (KPS) score ≥ 80; (3) patients who were at least 18 years old at the time of diagnosis, had a primary school education or above, and had sufficient audiovisual abilities to complete the questionnaire tests and intervention procedures; (4) patients with a life expectancy greater than 3 months. Patients were excluded if they met the following criteria: (1) patients with symptomatic brain metastases; (2) patients currently being treated for mental disorders; (3) advanced cachexia; (4) patients with other diseases that impact QoL, such as severe heart failure or disability.

Program

Figure 1 shows the research flowchart. Patients were orally introduced to the experiment by oncologists, and their informed consent was obtained. Patients were recruited from July 2022 to December 2022 and were hospitalized in the Oncology Department of the Hefei Cancer Hospital, Chinese Academy of Sciences, was assessed ($n = 74$). The questionnaires included DT, FACT-G, PFS, and tumor size data were also collected. Patients were followed until they completed 2 courses of chemotherapy, and tumor sizes were collected during follow-up. An oncologist evaluated the treatment

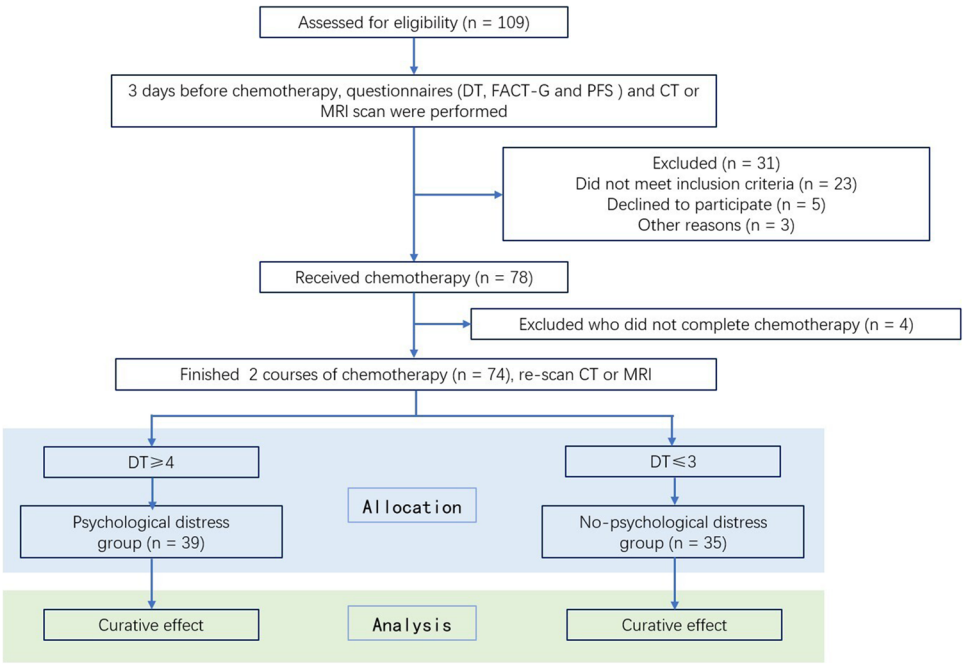

Fig. 1 Flowchart of the study. A total of 74 advanced GC patients were ultimately enrolled, and they were divided into psychological distress and no psychological distress groups according to their distress thermometer scale scores

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. Self-reported demographic and medical characteristics were collected at baseline. Participants were screened for psychological distress using the DT. The DT is a single-item tool using a 0 (no distress) to 10 (extreme distress)-point Likert scale resembling a thermometer. The patient rates his/her level of distress over the past week. In this study, patients with DT scores ≥ 4 were classified as having distress.

Treatment

All patients enrolled received 2 courses of chemotherapy-based systemic treatment, some in combination with targeted drugs and/or immunotherapy.

Primary outcome

The Response Evaluation Criteria in Solid Tumors (RECIST) criteria were used to evaluate the therapeutic effectiveness. 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. The objective response rate (ORR) was defined as the sum of PR and CR cases. The disease control rate (DCR) was defined as the sum of PR, CR, and SD cases.

Secondary outcome

The FACT-G is one of the most widely used patient-reported outcome measures in cancer research [19]. This questionnaire is designed for self-assessment. The FACT-G survey scores physical well-being (PWB; 7 items, score range 0–28), social/family well-being (SWB; 7 items, score range 0–28), emotional well-being (EWB; 6 items, score range 0–24), and functional well-being (FWB; 7 items, score range 0–28). All questions in the FACT-G use a 5-point rating scale (0 = not at all; 1 = a little bit; 2 = somewhat; 3 = quite a bit; and 4 = very much). The FACT-G total score is computed as the sum of the four subscale scores provided that the overall item response is at least 80% (i.e., at least 22 of the 27 items were answered) and has a possible range of 0–108 points.

The PFS has been validated in the Chinese population as a self-rating scale designed to assess CRF in cancer survivors [20] and covers four dimensions of fatigue: behavior/daily life (6 items), cognition (6 items), affect/emotional meaning (5 items), and feeling/body (5 items).

Each item was rated on a scale from 0 to 10, with a score of 0 being "not fatigued."

Statistical analysis

SPSS, version 22.0, software (http://spss.en.softonic.com/; IL, USA) was applied to conduct the statistical analysis. Waterfall plots were drawn with GraphPad Prism 5 (Graph Pad Software, Inc., CA, USA). The clinical baseline data were divided into the psychological distress and no psychological distress groups, adopting independent-sample *t*-tests for normally distributed data. The variables of sex, years of education, methods of treatment, KPS scores, and therapeutic effect were analyzed by the chi-square (χ^2) test in the two groups. Correlations between FACT-G and therapeutic effect, PFS, and therapeutic effect were analyzed using Pearson's correlation coefficient. All tests were two-tailed, and the significance level was set to 0.05.

Results

The clinical baseline data

A total of 74 advanced GC patients were confirmed to meet the criteria and were divided into two groups. The psychological distress group included 39 patients, and the no psychological distress group included 35 patients. As shown in Table 1, there were no significant differences in clinical characteristics, including age ($t=0.069$; $p=0.945$), sex ($\chi^2=3.422$; $p=0.668$), an education level ($\chi^2=0.537$; $p=0.764$), methods of treatment ($\chi^2=1.616$; $p=0.446$), and performance status ($\chi^2=2.440$; $p=0.118$).

Primary outcome

The clinical curative effect is shown in Table 2 and Fig. 2. None of the patients achieved CR in the two groups. In the psychological distress group, 8 patients had PR, 15 had SD, and 16 had PD. In contrast, in the no psychological

Table 1 The basic clinical characteristics of GC patients with or without psychological distress group

Characteristic	Psychological distress group ($n=39$)	No-psychological distress group ($n=35$)	t/χ^2	*p*-value
Age (years)	63.64 ± 11.99	63.46 ± 10.80	0.069	0.945
Sex, *n* (%)			0.184	0.668
Male	22 (56.41)	18 (51.43)		
Female	17 (43.59)	17 (48.57)		
Educational level, *n* (%)			0.537	0.764
Illiteracy	15 (38.46)	11 (31.42)		
Primary school	20 (51.28)	19 (54.29)		
Junior high school or above	4 (10.26)	5 (14.29)		
Methods of treatment, *n* (%)*			1.616	0.446
1	20 (51.28)	23 (65.71)		
2	7 (17.95)	4 (11.43)		
3	12 (30.77)	8 (22.86)		
KPS scores			2.440	0.118
80	28	19		
90	11	16		

*Methods of treatment: (1) chemotherapy, (2) chemotherapy + targeted therapy, and (3) chemotherapy + immunotherapy

Table 2 The efficacy of GC patients with or without psychological distress group

Therapeutic effectiveness	Psychological distress group	No-psychological distress group	χ^2	*p*-value
			6.324	0.042
Complete response	0	0		
Partial response	8	16		
Stable disease	15	12		
Progressive disease	16	7		

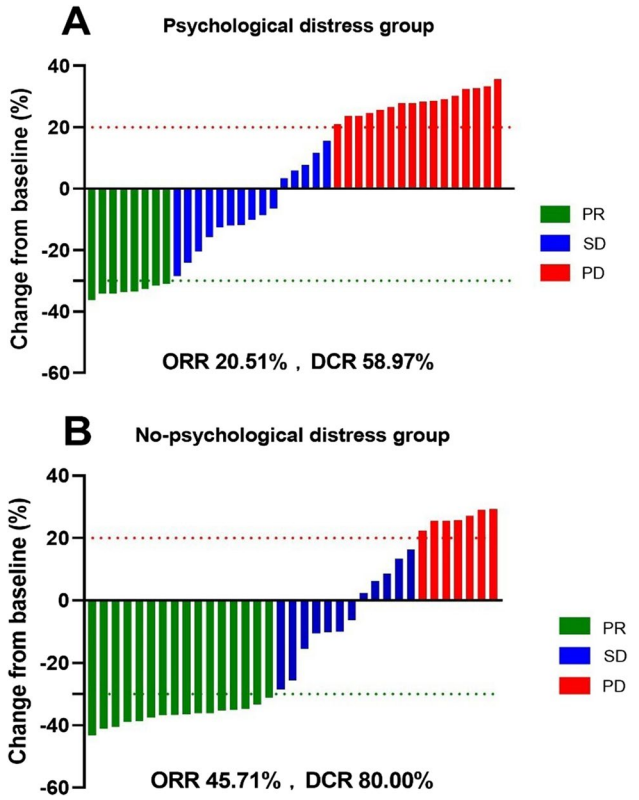

Fig. 2 Comparison of the therapeutic effect in advanced GC patients with or without psychological distress. **A** The therapeutic effectiveness in psychological distress group. **B** The therapeutic effectiveness in psychological distress group. PD, progressive disease; PR, partial response; SD, stable disease; ORR, objective response rate; DCR, disease control rate

distress group, 16 patients had PR, 12 patients had SD, and 7 patients had PD. The objective response rate and disease control rate of the psychological distress group were 20.51% and 58.97%, and those of the no psychological distress group were 45.71% and 80.00%, respectively. A significant difference in efficacy was found between the two groups ($\chi^2 = 6.324$; $p = 0.042$). Waterfall charts displaying the curative effects for both groups are shown in Fig. 2.

Secondary outcome

Table 3 shows the FACT-G scores of the two groups of patients. The total FACT-G score was significantly lower in the psychological distress group than in the no psychological distress group (50.41 ± 6.17 vs. 60.01 ± 7.94, $t = -5.882$, $p < 0.01$). Specifically, physical well-being (12.56 ± 3.76 vs. 15.77 ± 2.30, $t = -4.473$, $p < 0.01$), social/family well-being (16.23 ± 3.31 vs. 17.31 ± 3.11, $t = -1.445$, $p = 0.153$), and functional well-being (9.84 ± 4.23 vs 15.74 ± 5.05, $t = -5.462$, $p < 0.01$) were both lower than the no psychological distress group, but the difference in social/family well-be in scores was not statistically significant. Although the scores for emotional well-being (11.77 ± 2.91 vs. 11.26 ± 2.30, $t = 0.835$, $p = 0.407$) were slightly higher than those in the no psychological distress, there was no statistically significant difference.

Table 4 shows the PFS scores for the two groups. The total PFS score was significantly higher in the psychological distress group than in the no psychological distress group (5.75 ± 1.16 vs. 3.22 ± 0.75, $t = 11.231$, $p < 0.01$). The scores for all four items of PFS were higher in the psychological distress group than in the no psychological distress group and all were statistically different. The specific scores were as follows: behavioral/daily life CRF (6.50 ± 1.53 vs. 2.71 ± 0.92, $t = 13.028$, $p < 0.01$), emotional/affective CRF (5.95 ± 1.47 vs. 2.90 ± 0.93, $t = 10.765$, $p < 0.01$), sensory/physical CRF (5.49 ± 1.13 vs 3.80 ± 1.12, $t = 6.442$, $p < 0.01$), and cognitive CRF (5.08 ± 1.17 vs 3.48 ± 1.00, $t = 6.279$, $p < 0.01$).

As shown in Fig. 3, FACT-G ($p = 0.0035$, $r = -0.4568$) and PFS ($p < 0.0001$, $r = 0.6599$) correlated significantly with efficacy for patients in the psychological distress group. The FACT-G ($p = 0.0134$, $r = -0.4139$) of patients in the no psychological distress group correlated significantly with efficacy.

Table 3 FACT-G scores of GC patients in with or without psychological distress group

Item	Psychological distress group ($n = 39$)	No-psychological distress group ($n = 35$)	t	p-value
Physical well-being	12.56 ± 3.76	15.77 ± 2.30	-4.473	0.000†
Social/family well-being	16.23 ± 3.31	17.31 ± 3.11	-1.445	0.153
Emotional well-being	11.77 ± 2.91	11.26 ± 2.30	0.835	0.407
Functional well-being	9.84 ± 4.23	15.74 ± 5.05	-5.462	0.000†
FACT-G total score	50.41 ± 6.17	60.01 ± 7.94	-5.882	0.000†

†$p < 0.01$

FACT-G, Functional Assessment of Cancer Therapy-General

Table 4 PFS scores of GC patients in with or without psychological distress group

Item	Psychological distress group ($n=39$)	No-psychological distress group ($n=35$)	t	p-value
Behavior/daily life CRF	6.50 ± 1.53	2.71 ± 0.92	13.028	0.000†
Emotional/affective CRF	5.95 ± 1.47	2.90 ± 0.93	10.765	0.000†
Sensory/physical CRF	5.49 ± 1.13	3.80 ± 1.12	6.442	0.000†
Cognitive CRF	5.08 ± 1.17	3.48 ± 1.00	6.279	0.000†
Total CRF score	5.75 ± 1.16	3.22 ± 0.75	11.231	0.000†

†$p<0.01$

PFS, Piper Fatigue Scale

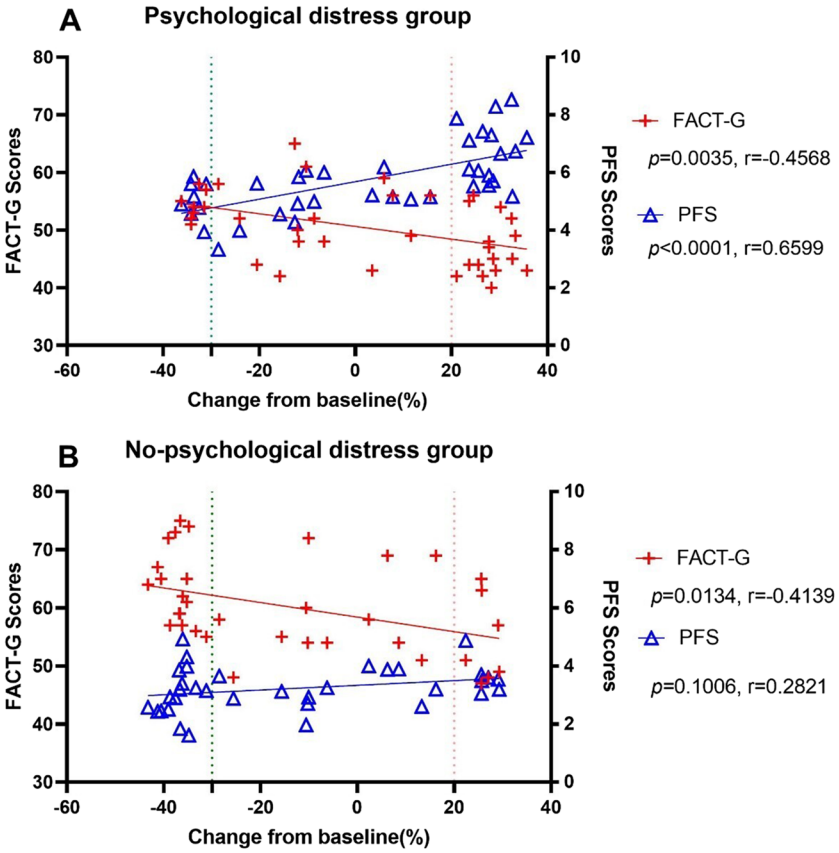

Fig. 3 Correlation of tumor size change with scale scores. **A** Correlation of tumor size change in the psychological distress group with FACT-G and PFS scores, respectively ($p=0.0035$, $r=-0.4568$; $p<0.0001$, $r=0.6599$). **B** Correlation of tumor size change in the no psychological distress group with FACT-G and PFS scores, respectively ($p=0.0134$, $r=-0.4139$; $p=0.1006$, $r=0.2821$). FACT-G, Functional Assessment of Cancer Therapy-General; PFS, Piper Fatigue Scale

Discussion

The present research investigated whether psychological distress was one of the risk factors influencing the prognosis of advanced GC patients who underwent chemotherapy. The authors found that advanced GC patients with psychological distress have a poorer QoL and more severe fatigue, and the objective response rate of advanced GC patients with psychological distress was worse than those of patients without psychological distress. The efficacy of patients in both groups was significantly correlated with QoL, and CRF in the psychological distress group was correlated with efficacy. It was found that the negative effects of psychological distress could be recognized in advanced GC patients with chemotherapy.

Palliative systemic treatment is an option to extend overall survival and although new systemic treatment modalities have improved survival in advanced GC, the 5-year survival rate is still below 30% [21, 22]. In clinical practice, the factors affecting the prognosis of advanced GC patients are complex, including differences in treatment methods, pathological staging of tumors, and the psychological status of patients. Lijuan Han found that anxiety and depression were among the factors affecting disease-free survival and overall survival in patients with gastric cancer after surgery [23].

Results from a Korean population-based survey of patients with stage IV gastric cancer showed that overall survival with psychological distress was lower than that of patients without psychological distress. And our latest study also found that survival of brain metastasis patients undergoing WBRT was negatively influenced by psychological distress [24]. These results were similar in that patient with advanced gastric cancer with psychological distress had poorer overall outcomes than patients without psychological distress when receiving chemotherapy-based systemic therapy [4].

With the change in the medical model from pure biomedicine to bio-psycho-social medicine, psychological distress has gradually become a concern involving the physical diseases themselves and the side effects of treatment [25]. Patients with advanced or metastatic gastric cancer often suffer from dysphagia, anorexia, nausea, and vomiting, and these problems can lead to psychological distress. Much of the psychological distress of cancer patients is associated with a decline in functioning and QoL, which can be exacerbated by a decline in QoL [26]. CRF has a devastating physical, mental, economic, and social impact, and it can be severe enough to seriously affect QoL during and after treatment [27]. Our findings found that fatigue was worse in patients with advanced GC with psychological distress. Several studies have found that CRF in cancer patients shows a significant positive correlation with psychological distress [28, 29]. And a previous review analysis based on predictors of distress in breast cancer suggested that CRF is one of the controllable symptoms associated with distress [30]. Therefore, we suggest that CRF on the table of patients with advanced GC receiving systemic therapy should be taken seriously and effective interventions should be made to alleviate the resulting psychological distress. The screening and assessment of psychological distress are important, and pertinent intervention measures should be implemented, which could improve the health outcomes of cancer patients [31].

The DT has demonstrated sufficient reliability as an NCCN-recommended tool for assessing psychological distress to assist clinicians in the identification and assessment of the degree of psychological distress in patients [18]. New or increased psychological distress in patients with advanced GC during treatment may be a consequence of fatigue from treatment or fear of death from advanced tumors. The impact of psychological distress on QoL, CRF, and therapeutic effectiveness during chemotherapy-based systemic therapy in patients with advanced gastric cancer has not been previously reported. This study confirms for the first time the negative impact of psychological distress on patients with advanced GC cancer receiving chemotherapy-based systemic therapy as a risk factor for treatment therapeutic effectiveness. The possible hypotheses on how psychological distress affects the therapeutic effectiveness of GC cancer patients are as follows. First, the presence of psychological distress is a risk factor for treatment non-adherence. A meta-analysis showed that non-adherence was higher in depressed patients compared to non-depressed patients [32]. Poorer patient adherence significantly reduces treatment efficacy. Second, chronic stress from psychological distress can lead to a body that can be in constant overdrive, leading to possible deleterious effects on the modulation of stress response and organ systems [33]. There is growing support that chronic stress-mediated activation of the hypothalamic–pituitary–adrenal axis (HPA), sympathetic nervous system (SNS), and microbiota-gut-brain (MGB) axis directly modulates the cancer profile of chronic exposure to multiple stress hormones such as glucocorticoids and catecholamines [34]. Third, immune dysfunction and changes in signaling pathways may lead to tumor progression. β-Adrenergic signaling has been found to reduce the number of cytotoxic T lymphocytes or their antitumor function, resulting in reduced cancer survival [35]. Finally, psychological distress may lead to tumorigenesis by stimulating an inflammatory response. Psychological distress was found to be associated with several inflammatory markers (white blood cell, C-reactive protein) [36] and increased expression of inflammatory factors (IL-6, IL-8, TNF-α, MCP-1, VEGF, MMP-2, MMP-9) enhanced tumor metastatic invasion [37]. Notably, TNF-α, IL-1, and IL-6 also mediated the development of CRF [38], which can and will negatively affect the QoL of gastric cancer patients [39]. Therefore, the biological mechanisms by which psychological distress affects the efficacy of chemotherapy in GC patients in this study can be further investigated from these aspects.

The modalities of ways to improve psychological distress include both non-pharmacologic and pharmacologic, but currently much attention is focused on interventions through non-pharmacologic approaches. A variety of non-pharmacological interventions regarding psychological distress, including methods based on positive thinking interventions [40, 41], talk/communication/cognitive behavioral therapy (CBT)-based methods [42], and psychological and psychosocial therapies [43], have shown improvement in heart distress due to a variety of cancers, including GC. In addition, studies based on breast cancer have shown that music interventions [44] as well as yoga [45] have a significant role in alleviating psychological distress as well as improving quality of life. Among pharmacologic therapies, much attention is being paid to the use of adrenergic receptors as actionable target targets, given the possible biological mechanisms mentioned in the previous section. Propranolol and the β2-adrenergic receptor (ADRB2)-specific antagonist ICI118,551 have been identified as having antitumor properties in GC by inhibiting the stress-regulated activation of the ERK1/2-JNK-MAPK pathway [46]. It is worthwhile to pay attention to the improvement of the efficacy of advanced gastric cancer by ameliorating psychological distress.

The limitations of this study should also be mentioned. Firstly, it was a single-center, small-sample study, and the sample was not selected to completely avoid the influence of some confounding factors. Second, no long-term follow-up study was conducted, and further follow-up is still needed regarding the effect of psychological distress on progression-free survival and overall survival of patients with advanced GC receiving chemotherapy. Thirdly, this study only found a negative effect of psychological distress on the efficacy of chemotherapy in advanced GC, and its further biological mechanisms are still unclear and need to be further investigated.

Conclusion

In summary, our results provide direct proof that psychological distress in GC patients affects the curative effect of systemic antineoplastic therapy. Moreover, we found that psychological distress is one of the factors affecting the QoL and CRF during systemic treatment in patients with advanced GC. This provides a theoretical basis for the intervention and improvement of the effect of efficacy through psychological factors in advanced GC patients.

Author contribution Conceptualization: Huaidong Cheng, Chen Gan, and Yongkang Zhang; methodology: Wen Li and Jian Xu; resources: Yongkang Zhang and Lulian Pang; writing—original draft preparation: Yongkang Zhang and Chen Gan; writing—review and editing: Chen Gan and Wen Li; and funding acquisition: Huaidong Cheng; Yongkang Zhang and Chen Gan contributed equally to this work. All authors have read and agreed to the published version of the manuscript.

Funding This work was supported by the grants from the National Natural Science Foundation of China (No. 81872504).

Data Availability The data that support the findings of this study are available from the corresponding author, Huaidong Cheng, upon reasonable request. All authors agree to provide data to the journal for review if needed.

Declarations

Competing interests The authors declare no competing interests.

Institutional review board statement The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of Research Ethics Committee of the Second Affiliated Hospital of Anhui Medical University (Number of Ethical Approval: 2012088).

Conflict of interest The authors declare no competing interests.

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