Peer Review File

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Reviewer A

Important research question to assess impact of CBT on colorectal cancer treatment side effects. At the manuscript exists only as a study protocol and does not contain data, recommend resubmitting once analysis is completed. Some points which may be relevant to your final manuscript:

Comment 1: Clarify the method of change hypothesized as this is unclear (mediated relationship - CBT will decrease depression which will impact tumor markers which in turn decreases side effects?)

Reply 1: In theory, CBT can reduce the side effects of chemotherapy by reducing the level of depression and anxiety. Whether it can actually reduce the side effects of chemotherapy is the content of this study, because there is a lack of evidence on the reduction of CBT on the side effects of chemotherapy so far.

The effect of CBT on immune function of cancer patients has been studied extensively in breast cancer patients with sufficient evidence, while there is less research and insufficient evidence in CRC patients. Therefore, the effect of CBT on immune function of CRC patients is also one of the contents of this study. The underlying biological mechanism of CBT (CBT will improves anxiety and depression, which will enhance immune function and in turn reduce chemotherapy side effects?) is the subject of this study. The level of tumor markers is only one of the observational measures.

Changes in the context: "In theory, CBT can reduce the side effects of chemotherapy by reducing the level of depression and anxiety." (see **Page 4, line 108-109**)

"Psychological interventions (including CBT) can improve immune function in cancer patients." (see **Page 4, line 114-115**)

"We also try to explore the underlying biological mechanism of CBT." (see **Page 4, line 120-121**)

Comment 2: Inclusion states only patients with Stage IV disease are included but treatment intent (management v cure) is much different and the medical course could be more rigorous and potentially not impacted as greatly by CBT. Also end of life and quality of life concerns should be addressed in this population but don't see mention of that in the CBT intervention.

Reply 2: In order to keep the patient group homogenous, the study only includes stage IV colorectal cancer going for first-line chemotherapy. The patients receiving mixing adjuvant and neoadjuvant chemotherapy will not be included.
And We will not include patients end of life, because CBT is not a good psychological intervention at this stage.
Changes in the context: "Receive adjuvant chemotherapy, neoadjuvant chemotherapy and immunotherapy" (see **Page 5, line 159**)

Comment 3: Need to control or assess for impact of any SSRI use as psychotropics may have dual purposes which could affect both mood and side effects (i.e. lorazepam for anxiety and nausea).
Reply 3: We will not include patients with a history of anxiety and depression and who are currently taking SSRIs, nor will we include patients with severe anxiety and depression, because such patients would be more appropriate to consider SSRIs first.

Comment 4: Encourage some measure of adherence to medical regimen as this too may be a mediated effect on outcomes (i.e. Arrieta, Ó., Angulo, L. P., Núñez-Valencia, C., Dorantes-Gallareta, Y., Macedo, E. O., Martínez-López, D., ... & Oñate-Ocaña, L. F. (2013). Association of depression and anxiety on quality of life, treatment adherence, and prognosis in patients with advanced non-small cell lung cancer. Annals of surgical oncology, 20, 1941-1948.
Reply 4: Thanks for reviewer's constructive comments. We will supplement the treatment adherence program.

Comment 5: Depending on results may want to consider that distress and physical symptoms do not have a direct correlation. Patient in the CBT intervention may still experience similar symptoms as those in the control but with improved coping may feel less distressed by them.
Reply 5: Thanks for reviewer's constructive comments. In the data analysis phase, we will analyze correlations such as physical symptoms, mood and immune function.

Reviewer B

The effect of cognitive behavioral therapy on chemotherapy-induced side effects and immune function in colorectal cancer patients undergoing chemotherapy:
Study protocol for a randomized controlled trial

Overview: This is a study protocol for an on-going single-site psychosocial interventional trial for patients with stage 4 colorectal cancer. This study is interesting and could provide evidence to support the psychological management of patients with cancer. However, it currently lacks many details. Authors could provide more information about the rationale for study decisions. Additionally, authors could highlight the strength of this study in its location, mainland China, if this question has yet to be explored in this region/cultural demographic. There is potential with this study protocol and I hope the authors take the opportunity to improve it to contribute in this important area.
In addition to these primary concerns, some specific comments follow:

Abstract:
Comment 1: Methods: are the sessions weekly? Biweekly? Please include some aspect of the duration; this will help anchor T1 relative to baseline (currently unclear).
Reply 1: Every intervention session will last for 60 minutes (45 minutes for CBT and 15 minutes for relaxation training) and will be conducted every 2–3 weeks within the period of each chemotherapy course. The intervention is performed every time the patient comes to the hospital for chemotherapy, so the intervention time is determined by the patient's chemotherapy regimen. Some patients receiving chemotherapy every 3 weeks and some patients receiving chemotherapy every 2 weeks.
Changes in the context: "every 2–3 weeks" (see **Page 2, line 48**)

Comment 2: Methods: could the authors be more specific about their outcomes of interest related to the primary aim? Could they include any examples of which tumor markers will be included as outcomes?
Reply 2: The primary goal of the study is to determine the effect of CBT on chemotherapy-induced side effects in CRC patients. Chemotherapy-induced side effects will be evaluated using the M.D. Anderson Symptom Inventory-Gastrointestinal Cancer Module (MDASI-GI). Some tumor markers will be included as outcomes, for example, AFP, CEA, CA19-9, CA125 and so on.

Comment 3: Discussion: please modify language suggesting the effects of the study (e.g., "our study provides evidence"), as the trial has not been conducted or reported on yet.
Reply 3: Thanks to Reviewer for reminder, we made changes in the manuscript.
Changes in the context: "our study will provide clinical evidence regarding whether CBT should be generalized in clinical treatment and the extent to which CBT reduces chemotherapy-induced side effects for CRC patients." (see **Page 2, line 58-60**)

Comment 4: Strengths/Limitations: #3 – please include who will be delivering this intervention within this multidisciplinary team.
Reply 4: Two psychotherapists will deliver the intervention.

Introduction: The introduction is clear and concise; however, authors would benefit from adding more information about immune and inflammation status related to their outcomes of interest. Much prior evidence in other cancer types exists to relate CBT to improvements in physiological measures. This would strengthen the gap for the current study in CRC patients.

Comment 5: Paragraph 1: the location of the study will be in China, so authors should include relevant statistics related to CRC in the geographic area where the study will be conducted vs. the U.S.
Reply 5: Thanks to Reviewer for reminder, we have added some information in the manuscript.
Changes in the context: **"**At present, the incidence of colorectal cancer ranks second among all malignant tumors in China." (see **Page 3, line 84-85**)
"The number of new cases in 2022 is estimated to exceed 590,000." (see **Page 3, line 86-87**)

Comment 6: Lines 88-89: please modify the grammar of this sentence as it seems these rates apply to most patients overall with CRC, not a specific study, etc.
Reply 6: Thanks to Reviewer for reminder, we have modified the grammar.
Changes in the context: "Increasing evidence suggested that CRC patients have a high risk of psychological disorders" (see **Page 3, line 91-92**)

Comment 7: Line 103: "However, the mechanism of CBT as a treatment for CRC patients remains unclear." Several psychological models and theories exist that could explain this mechanism. Are authors referring to specific outcomes that CBT could improve? At present, this sentence is not entirely accurate of the existing literature.
Reply 7: Thanks to Reviewer for reminder, we have modified the expression in the manuscript.
Changes in the context: **"**We also try to explore the underlying biological mechanism of CBT." (see **Page 4, line 120-121**)

Comment 8: Authors should include the following study in their introduction, as a similar protocol among patients with metastatic CRC was recently published: Baussard L, Cousson-

Gélie F, Jarlier M, et al. Hypnosis and cognitive behavioral therapy with online sessions to reduce fatigue in patients undergoing chemotherapy for a metastatic colorectal cancer: Rational and study protocol for a feasibility study. Front Psychol. 2022;13:953711. Published 2022 Jul 27. doi:10.3389/fpsyg.2022.953711

Reply 8: Thanks to Reviewer for reminder, we have learned this article and incorporated it into the references.

Changes in the context: "Cognitive behavioral therapy (CBT) has been demonstrated to be effective in reducing depressive and anxiety symptoms in cancer patients (22,23), and alleviate fatigue in cancer patients (24)." (see **Page 4, line 106-108**)

"Baussard L, Cousson-Gélie F, Jarlier M, et al. Hypnosis and cognitive behavioral therapy with online sessions to reduce fatigue in patients undergoing chemotherapy for a metastatic colorectal cancer: Rational and study protocol for a feasibility study. Front Psychol. 2022;13:953711." (see **Page 16, line 508-511**)

Methods:

Comment 9: The methods are brief and currently lack some important details of the study. How will the study team adapt the intervention to patients with varying lengths of chemotherapy? Do participants have to enroll prior to the start of chemotherapy? Will they be excluded for other types of treatment receipt (e.g., radiation, immunotherapy received prior to chemo)? Why is eligibility limited to stage 4? Stage has not been mentioned at all throughout the introduction and should be referenced if limiting patient enrollment by stage. If patients may have received other treatments first, how will existing non-chemo related symptoms be managed related to the primary aim? Additionally, though the primary aim of the study is to assess CBT effect on chemo side effects, the study was powered for detecting a change in IL-1. Authors should power their sample based on the primary outcome, MDASI-GI.

Reply 9: Thanks to Reviewer's constructive comments. The participants will be enrolled prior to the start of chemotherapy. The patients receiving mixing adjuvant, neoadjuvant chemotherapy and immunotherapy will not be included. In order to keep the patient group homogenous, the study only includes stage IV colorectal cancer going for first-line chemotherapy. We have added some information in the manuscript.

Changes in the context: "Receive adjuvant chemotherapy, neoadjuvant chemotherapy and immunotherapy" (see **Page 5, line 159**)

Comment 10: Intervention: is this intervention based on other evidence-based CBT regimens? If so, this should be cited appropriately in the methods section. Is the intervention conducted

in-person? The description of the intervention is currently too brief. Please include additional aspects that could adhere to the TIDiER guidelines.

Reply 10: Thanks to Reviewer's constructive comments. The intervention is based on evidence-based CBT regimens for breast cancer patients. We further refined the intervention in the manuscript.

Changes in the context: "The intervention will be performed in the ward's post-operative recovery room each time the patient comes in for chemotherapy. Patients randomly assigned to the CBT group will receive usual oncology care (including nutrition assessment, stoma care, observation of chemotherapy drug adverse reactions, etc.) in addition to 8 sessions of group-based intervention (3–6 participants per group). Group is open because patients have different chemotherapy regimens and it is difficult for patients in the same group to be hospitalized for chemotherapy at the same time every time." (see **Page 6, line 180-186**)

Comment 11: Control group: is any of this information also included for the intervention group? Is this a control condition that has been used previously? Authors describe this as usual oncology care – will other care team member present the information in the control groups or will the same psychologists who delivered the intervention provide the control group? Please clarify.

Reply 11: Intervention group will not receive four sessions of health education. Nursing instructions on diet, exercise, etc., are given to patients before they leave the hospital after surgery. Caregivers may know who is in the intervention group and who is not. However, this does not affect the assessment, because the evaluator does not know the grouping. Psychologists who delivered the intervention will not provide the information in the control group.

Comment 12: Measures: if some measures are collected at the end of each chemo cycle, how will the study team manage cycles of differing days/lengths? Significantly more information is needed right now to fully conceptualize the analytic plan related to the study procedures.

Reply 12: Data from the first follow-up will be collected at the end of the last intervention, including assessment of relevant scales and detection of biochemical indicators. The second and the third follow-up visits will be made during the patient's return visit to the hospital.

Comment 13: Randomization and blinding: it is noted that the research assistant conducting assessments will be blinded but it is currently unclear exactly how patients will complete assessments (e.g., in person, paper, website based, etc.).

Reply 13: Patients will complete assessments through a paper questionnaire. The data will be collected by trained research assistants and recorded on case report forms.

Discussion:

Comment 14: At present, the discussion lacks any information about the clinical implications of the study. The authors could be more clear about how this current study will close a gap in the literature for CRC patients and chemo-related side effects.

Reply 14: Thanks to Reviewer's constructive comments. We further refined the discussion in the manuscript.

Changes in the context: "Moreover, some studies have examined the positive impact of CBT on fatigue reduction in cancer patients (55). Therefore, CBT maybe a promising method that has the potential to reduce the side effects of chemotherapy. In addition, CBT has been shown to improve immune function in other patients, such as HIV and sleep disturbance (56,57), but there have been few studies in CRC patients." (see **Page 13, line 412-417**)

Reviewer C

Comment 1: The abstract clearly states the importance and procedures of the RCT. It is recommended to bring more clarity to what exactly the primary outcome refers to. Do you intend to measure the improvement of the chemotherapy-induced side effects? Short-term or long-term ones? Which are they? Please specify. Regarding the discussion section, the authors state that they have evidence to use CBT in clinical treatment, however, no results are presented in the abstract. If such a statement is made, it needs to be based on the outcomes of the study.

Reply 1: Chemotherapy-induced side effects will be evaluated using the M.D. Anderson Symptom Inventory-Gastrointestinal Cancer Module (MDASI-GI), which includes 13 core symptom items, five gastrointestinal cancer-specific symptom items, and six interference items. Follow-up lasted up to 6 months after the intervention. Therefore, the improvement of side effects of chemotherapy will be observed for 6 months.

Reviewer D

Introduction:

Comment 1: "It was the third most diagnosed cancer and the second most common cause of cancer-related death in the United States in 2020" -- what about China?

Reply 1: Thanks to Reviewer for reminder, we have added some information in the manuscript.

Changes in the context: "At present, the incidence of colorectal cancer ranks second among all malignant tumors in China." (see **Page 3, line 84-85**)
"The number of new cases in 2022 is estimated to exceed 590,000." (see **Page 3, line 86-87**)

Measures:

Comment 2: Is GAD-7 an instrument for the assessment of Generalized anxiety disorder? Anxiety symptoms are common among cancer population but not generalized anxiety disorder. It seems more suitable for this purpose to use HADS (designed for clinical populations with physical symptoms or conditions). HADS is validated in chinese cancer population (Li, Q., Lin, Y., Hu, C., Xu, Y., Zhou, H., Yang, L., & Xu, Y. (2016). The Chinese version of hospital anxiety and depression scale: psychometric properties in Chinese cancer patients and their family caregivers. European Journal of Oncology Nursing, 25, 16-23.)

Reply 2: GAD-7 is a widely used anxiety screening scale, which is used to evaluate the anxiety of the test subjects. It is convenient and fast to evaluate, and has good reliability and validity. It is widely used to screen for anxiety in general hospital patients, including those with gastrointestinal tumors. (Yu Wang， Ｒan Chen，Lan Zhang. Evaluation of the reliability and validity of the generalized anxiety disorder 7-item scale among inpatients in general hospital. J Clin Psychiatry. 2018,28(3):168-171.) (Harms J, Kunzmann B, Bredereke J, et al. Anxiety in patients with gastrointestinal cancer undergoing primary surgery. J Cancer Res Clin Oncol. 2023 Sep;149(11):8191-8200.)

Comment 3: Follow-up assessment: could the authors explain why they are not taking measures of side effects (MDASI-GI) on follow-up timepoints? This is their primary outcome, and their primary hypothesis is that CBT is able to reduce side effects of chemotherapy more than TAU.

Reply 3: Thanks to Reviewer for reminder. We will evaluate the side effects on follow-up timepoints.

Changes in the context: "Contents: all baseline measures except SSRS" (see **Page 10, line 317**)

Comment 4: Sample size estimation: "Sample size calculation was based on the results of a previous RCT conducted among breast cancer patients to determine the effect of cognitive therapy on immune function (41)". It seems not truly appropriate because the authors are calculating N based on the variable immune function, which is not their primary outcome. Is there any study on the effects of CBT on side effects of chemotherapy? You can find some examples on "Daniels, S. (2015). Cognitive behavior therapy for patients with cancer. Journal

of the advanced practitioner in oncology, 6(1), 54". Even if the authors cannot find studies about the effects of CBT on chemotherapy side effects it would seem more appropriate to find some research which tests the effect of any other psychotherapy on chemotherapy side effects (their primary outcome) in order to calculate N. If any of this is possible, I would recommend the authors to design a pilot study with a small sample and obtain data from it to calculate final sample size.

Reply 4: Thanks to Reviewer's constructive comments. The study Reviewer's mentioned is about the effects of CBT on fatigue in cancer patients. There are many studies on the effect of psychological intervention (including CBT) on fatigue of tumor patients, and the results are relatively positive. However, there are few studies on the effect of psychological intervention on side effects of chemotherapy, and no relevant studies have been found so far. Therefore, the sample size cannot be calculated by referring to the relevant indicators of side effects of chemotherapy. Since CBT is widely used in breast cancer, we chose a study on the effect of CBT on immune function in breast cancer patients as a reference to calculate the sample size.

Comment 5: Statistical analysis: If the authors have a superiority hypothesis, they should use a one-sided analysis.

Reply 5: Thanks to Reviewer for reminder. We will use one-sided analysis in data analysis.

Comment 6: Given that also psychotherapy can have side effects I recommend the authors to register any side effect they can have in their study and report them. It is very important to the scientific community.

Reply 6: Thanks to Reviewer's constructive comments. If a patient reports an adverse reaction of psychotherapy, we will record it in detail.

Comment 7: It seems to me a promising study, I encourage the authors to finish the study and publish the effectiveness results. Then, I encourage the authors to continue investigating on action mechanisms, which nowadays seems to be more important than effectiveness itself, and answer the question "which components of the therapies work and for whom?"

Reply 7: Thank you very much for your positive comments, your question is also very important to me, and it is also the answer I want to get in the study.

Reviewer E

1. Abstract (200~350 words)

Please extend the content of the Background. This paragraph should contain 'study background' and 'study objective'.

38 **Abstract**

39 **Background:** Colorectal cancer (CRC) was one of the most widely diagnosed cancers
40 in the United States in 2021. CRC patients may experience significant psychological
41 stress and are susceptible to depression and anxiety. Previous studies have shown that
42 cognitive behavioral therapy (CBT) can reduce fatigue and improve quality of life
43 among breast cancer patients. However, as a non-pharmaceutical treatment, it remains
44 unclear whether CBT improves chemotherapy-induced side effects and immune
45 function in CRC patients.

Reply: Thanks to editors for reminder. We have made changes in the manuscript.

Changes in the context: "In this study we will conduct a randomized controlled trial (RCT) among CRC patients undergoing chemotherapy to determine whether CBT can reduce the side effects of chemotherapy and improve the immune function of CRC patients." (see **Page 2, line 46-49**)

2. Reference/citation

a. Ref (44) is not cited in the main text. Please check and revise.

*Please note that the references should be cited in order of their appearance in the text.

Reply: Thanks to editors for reminder. We made changes in the manuscript.

Changes in the context: "Sample size calculation was based on the results of a previous RCT conducted among breast cancer patients to determine the effect of cognitive therapy on immune function (44)." (see **Page 10, line 313-315**)

b. Please check if more studies should be cited in this sentence. Please revise them to "a study" or to give more than one reference in this sentence.

"some studies have examined the positive impact of CBT on fatigue reduction in cancer patients (55)."

Reply: Thanks to editors for reminder. We made changes in the manuscript.

Changes in the context: "Moreover, some studies have examined the positive impact of CBT on fatigue reduction in cancer patients (24,55)" (see **Page 12, line 408-409**)