Effectiveness of combined nutrition, exercise and psychological interventions in patients with malignancy: A randomized controlled trial

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ABSTRACT

Background and Objectives: Patients with malignancy often have a poor prognosis and dismal quality of life. This study aimed to evaluate whether a combined nutrition, exercise, and psychological intervention could improve these outcomes. **Methods and Study Design:** In an open-label, randomized controlled trial at the First Hospital of Hebei Medical University (Oct 2021–Jun 2022), 90 patients were assigned (1:1) to a treatment group receiving 6-month cyclic combined assessments and interventions, or a control group receiving assessments only. Body composition, hand grip strength (HGS), 6-minute walk test (6MWT), Hospital Anxiety and Depression Scale (HADS), Patient Health Questionnaire-9 (PHQ-9), and quality of life were compared at baseline and 6 months. Data were analyzed using SPSS 21.0, with $p<0.05$ considered significant. **Results:** 90 people were enrolled, and 80 people have completed the study. Compared to controls, the intervention group showed significantly lower nutritional risk (10.00 % vs. 100.00 %, p <0.001) and malnutrition rates (22.50 % vs. 100.00 %, p <0.001). Significant improvements were observed in BMI, muscle mass, phase angle, HGS, and 6MWT distance (all p <0.001). HADS and PHQ-9 scores decreased (p <0.001). Quality-of-life scores (physical, role, emotional, social function, overall health) improved, while symptom scores (fatigue, pain, nausea/vomiting, etc.) decreased markedly (p <0.05). The control group exhibited opposite trends. **Conclusions:** Combined nutrition, exercise, and psychological interventions effectively improve nutritional status, physical and psychological well-being, and quality of life in patients with malignancy, potentially enhancing treatment tolerance and promoting rehabilitation.

Key Words: malignancy, nutrition support, home exercise, psychological intervention, body composition

INTRODUCTION

Malignant tumors, as one of the major public health problems in the world, have seriously threatened human life and health, and their morbidity and mortality rates continue to rise. Data from the Chinese Cause of Death Surveillance System show that malignant tumors deaths accounted for 23.87% of all deaths among residents, ranking first among urban residents and third among rural residents in China in 2020,[1] and according to the ASCO-2020 Global Cancer Statistics Report: Malignant tumors have become the first cause of death in China.[2] Therefore, there is an urgent need for effective interventions to improve the prognosis of malignant tumors, especially in the first-line setting.

At present, there is no clear and accepted concept about malignant tumors rehabilitation in the rehabilitation medical field. Malignant tumors rehabilitation involves multiple disciplines and should reflect the principle of whole course, comprehensive and full staff, namely the concept of multi-disciplinary team (MDT), which is a process of comprehensive and full management of malignant tumors patients. It is a medical and social behaviors performed by an oncologist, psychiatrist, nutritionist, rehabilitation therapist, rehabilitation nurse, and the patient's family.

A study showed that the combination of early nutritional intervention and psychological palliative intervention can improve the quality of life of patients with metastatic non-small-cell lung cancer and reduce the probability of depression, it can also improve patient outcomes and prolong overall survival by up to two months.[3] Another study showed that the combination of early nutritional intervention and psychological palliative intervention can improve the prognosis of patients with advanced esophageal malignant tumors and gastric malignant tumors and prolong overall survival by nearly three months.[4] Multi-modality pre-rehabilitation programmes (including physical, nutritional and psychological) seem to be more effective than single-modality pre-rehabilitation programmes, which is why three-pronged rehabilitation strategies are being advocated. Malnourished gastrointestinal cancer patients undergoing surgery bear high nutritional risk, and Oral nutritional supplements (ONS) can significantly improve health outcomes.[5] Malignant tumors multimodal rehabilitation has been paid more and more attention, but there is still no research on nutrition + exercise + psychology "triple multimodal rehabilitation". The multimodal rehabilitation model of malignant tumors has been paid more and more attention, but there is no research on the "triple multimodal rehabilitation" model of nutrition + exercise + psychology. Therefore, we carried out a single center, multidisciplinary cooperation, randomized controlled clinical study to analyze the impact of whole-process multi-mode rehabilitation management (hospital-home, nutrition-exercise and psychology) on the quality of life of malignant tumors patients, in order to provide scientific reference and value for promoting the rehabilitation of malignant tumors patients.

MATERIALS AND METHODS

Study design

This study was a single-center, multidisciplinary, randomized controlled trial performed at the First Hospital of Hebei Medical University. The trial protocol was approved by the ethical review board of the First Hospital of Hebei Medical University (ethics number: 20210752)

and was performed in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines, as defined by the International Conference on Harmonization. No changes were made to the study design after the trial began. All participants provided written informed consent before study participation. This study has been registered at the Medical Research Registration and Filing Information System of the National Universal Health Security Information Platform(registry number: MR-13-24-022431).

Population

Only inpatients were considered for inclusion. Eligible patients had histologically or cytologically confirmed malignant tumors, were 18 years or older, were at nutritional risk (Nutrition risk screening 2002 [NRS2002] scale score ≥3), had an estimated life expectancy of more than 12 months, and had adequate cognitive and reading abilities. We excluded patients with symptomatic brain metastases, poor performance status, a contraindication for exercise, or those currently receiving treatment of a mental disorder.

Sample size calculation

The sample size was calculated based on the primary outcome of PG-SGA score change before and after intervention. Assuming a mean difference of 3.0 points (effect size d = 0.80, large clinically meaningful effect), a type I error (α) of 0.05 (two-sided), and a statistical power of 80% (1−β = 0.80), we estimated that 40 participants per group (total 80) would be sufficient to detect the intervention effect. Considering a 10% dropout rate, we finally recruited 90 patients (45 in each group).

Setting and recruitment

From 1 October 2021 to 1 December 2021, oncologists at two departments of medical oncology screened patients with malignant tumors and provided study information to eligible patients. Dietitians visited patients who wanted to take part in further trials and agreed to provide further information. Patients who consented were scheduled for a study visit at hospital and administered baseline assessments. Eligible patients were randomly assigned to the intervention group (multidisciplinary supportive care combined with the standard anti-tumor care) or control group (only standard anti-tumor care) in a 1:1 ratio. A computer-generated random sequence was produced by an independent statistician not involved in patient enrollment or assessment. The allocation sequence was concealed in sequentially numbered, sealed, opaque envelopes. Envelopes were opened immediately upon enrollment

of each participant to assign group allocation, ensuring strict allocation concealment and reducing potential selection bias (Figure 1).

Anthropometric measurements

The patient's height and weight were measured using a portable fully automatic height and weight meter (BSM370®; South Korea). Patients were instructed to remove any heavy clothing (such as coats) and shoes in the morning on an empty stomach, and stand still on the weighing scale, with hands by their sides. The upper arm circumference and calf circumference were measured using a measuring tape and the skinfold thickness of the triceps muscle was measured using a skinfold thickness gauge.

Interventions and procedures

Usual care

All patients were treated for anti-tumor treatment such as chemotherapy and radiotherapy at the Department of Oncology, the First Hospital of Hebei Medical University. Patients in the treatment group would receive assessment and intervention of nutrition, exercise and psychological, while patients in the control group would only receive assessment of that.

Nutrition assessment and intervention

Nutritional assessment were completed by dietitians and included nutritional risk screening (NRS), nutritional assessment, information on dietary intake and body Composition Analysis. The NRS was defined by NRS2002, patients with a score of ≥3 were classified as nutritionally at-risk. The nutritional assessment was defined by Patient-generated Subjective Global Assessment (PG-SGA) with the following classification: PG-SGA grade A (0-1 points) was good nutrition; PG-SGA grade B (2-8 points) was suspected or moderate malnutrition; PG-SGA grade C (≥9 points) was severe malnutrition.[6] The information on dietary intake including patients energy and protein intake was evaluated by 24-hour dietary survey, and patients were instructed to fill out the Home Food Diary. Bioelectrical impedance analysis (BIA) was used to measure body composition (AiNST-CNDS20® Body Composition Analyzers; China). Nutritional intervention were conducted by dietitians and included nutrition education, dietary guidance and enteral nutrition supplemented (with a total energy of 25-35 kcal/kg-d and 1.0-1.5 g/kg-d of protein, including an intact protein enteral nutrition preparation [Beikangsu of AINST, China] and a whey protein preparation [Whey Protein of AINST, China]).

Exercise assessment and intervention

Exercise assessment was completed by rehabilitation therapists and included hand grip strength (HGS), 6-minute walk test (6MWT), 6-metre walking test (6WT) and five-times sit-to-stand test (5XSTS). The HGS was measured in the dominant hand by using a Grip Strength Meter (RH-WLJ®; China), with the arm in extension and in the vertical axis, while, for patients who couldn't sit or stand, HGS was measured in the supine position with the engaged arm extended. The 6MWT was performed on a 50 m indoor track, and patients were instructed to walk as far as possible in 6 mins at most, rehabilitation therapists calculated the walking distance. The 5XSTS was performed on a standard armless chair, and patients were told to complete 5 sit-to-stand maneuvers as fast as possible with the arms folded in front of the chest. Exercise intervention were conducted by rehabilitation therapists, patients were guided to get resistance exercise with individualized exercise programs according to their physical function. The resistance exercise program primarily consists of five modes of motion, including knee-extensor exercise, sitting-up exercise, padded foot exercise, straight‐leg raising exercise and side‐leg raising exercise (Figure 2), patients were required exercising at least 3 times per day and 30 cycles every time. Patients were recorded the number of steps walked per day to evaluate physical activity by using pedometers (CW10C®; China). The primary target of the number of daily steps was settled according to the average number of steps walked during the screening period as follows: If a patient average daily steps were ≤2000, the target steps was 2000. If a patients average daily steps were 2000-8000, the target steps was the average steps adding 2000. If a patients average daily steps were ≥8000, then the patient was educated to maintain his/her current level of PA.

Psychology assessment and intervention

Psychology assessment were completed by psychotherapists and included Hospital Anxiety and Depression Scale (HADS) and Patient Health Questionnaire 9 (PHQ-9). The HADS comprises 14 items and consists of an Anxiety subscale (HADS-A) and a Depression subscale (HADS-D), patients' scores of HADS-A and HADS-D above 9 were classified as having depression and anxiety, respectively.[7] The PHQ-9 is a questionnaire designed to screen for depression[8,9] and including 9 items correspond to the DSM-5 diagnostic criteria for major depressive disorder.[10] The PHQ-9 score ranges from 0 to 27, and per item is scored from 0 to 3, 0 = not at all, 1 = several days, 2 = more than half of the days and 3 = nearly every day. "Major depression" is diagnosed if five or more of item scores ≥2 points.[11] Psychology

intervention were conducted by psychotherapists, and included Home-based Music Therapy, WeChat Groups Collective Education, online psychosocial intervention and psychotropic medications intervention. Home-based Music Therapy: firstly, psychotherapists explained the scientificity and necessity of music therapy to the patients, so that the patients had a sense of trust and dependence. Then chose music that was appropriate for cancer patients and Placed in the WeChat Public Accounts, so patients could choose the music within the prescribed emotional range to Listen. The music mainly included Chinese Relaxing Music, Classical Relaxing Music, English Relaxing Music, Religious Relaxing Music and Japanese Relaxing Music. Music Therapy should take about 30 minutes each time with 3-Times-Daily.

Quality of life assessment

The 30-item European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTCQLQ-C30) was a systematic evaluation approach to assess the quality of life of patients with malignancy. The quality of life assessed by oncologists using the Chinese version of EORTC QLQ-C30 (version 3).[12] The questionnaire included 30 items and divided into five functional areas (physical function, role function, emotional function, cognitive function, and social function), three symptomatic areas (fatigue, nausea/vomiting, and pain), one score for the overall quality of life, and six single measurement items (dyspnea, insomnia, appetite loss, constipation, diarrhea, financial problems). Calculation of points: Raw score (RS), RS = (Q1 + Q2 + …Qn) / n; Standard Score (SS), SS = [1 - (RS - 1) / R] x 100 (five functional areas) and SS = [(RS - 1) / R] x 100 (others), the R was full range of every item score, Standard Score were used in this study. The scoring rules: the higher scores indicated better functioning and quality of life for five functional areas and the overall quality of life, while the higher scores indicated more symptoms or problems (worse quality of life) for three symptomatic areas and six single measurement items.

Other measurement indicators

The detection indexes were as follows: routine blood tests, biochemical tests and liver and kidney function tests. Hypoproteinemia was defined as a serum albumin concentration <40 g/L. Anemia was defined as hemoglobin <130 g/L for men and <115 g/L for women.

Follow up

Follow up of the patients were completed by medical commissioner

The follow up period for the patients was every five days by telephone or WeChat for 6 months. The diet ingestion, exercise, listening to music and adverse effects were recorded for the commissioner, adverse effects mainly included nausea, vomiting, poor appetite, constipation, diarrhea and fatigue and so on.

Adherence to the multi-component intervention was monitored through regular telephone follow-ups and standardized record forms, which documented participants' implementation of resistance exercise, music therapy, dietary targets, daily step counts, and any adverse events. Although the completion of each intervention component was recorded in detail, the complexity and multi-domain nature of the intervention prevented these data from being summarized and presented as a unified quantitative adherence rate or numerical score.

Statistical analysis

Statistical analyses were performed using SPSS 21.0. The measurement data conforming to the normal distribution were expressed as mean ± standard deviation ($\bar{x} \pm s$), student's t-test was used for comparison between two groups, and paired t-test was used for comparison between pre-post differences. The abnormally distributed measurement data were expressed as median (interquartile range) [M (Q)], the Wilcoxon rank-sum test was used for comparison between two groups, and Wilcoxon signed-sum test was used for comparison between pre-post differences. Count data were expressed as frequencies (percentages), and the $\chi 2$ test was used for comparison between two groups and pre-post differences. $p < 0.05$ was considered a statistically significant difference.

Given the significant between group difference in baseline weight ($p = 0.028$), analysis of covariance (ANCOVA) was performed for all outcome variables at the 6 month follow up, with baseline weight and the baseline value of each outcome as covariates to adjust for potential confounding. Between group differences are reported using both unadjusted and adjusted values to confirm the robustness of intervention effects.

Since the primary outcome was clearly defined a priori, and secondary outcomes were interpreted in a supportive, exploratory manner, we did not apply a strict multiplicity adjustment to avoid an excessive loss of statistical power. However, we acknowledge the potential for inflated Type I error and interpret all findings with appropriate caution.

RESULTS

Between October 1, 2021 and December 1, 2021, a total of 136 patients with malignancies were screened for participation and 90 were enrolled and randomly assigned to treatment group (n = 45) or control group (n = 45; Figure 1). Finally, 80 patients (40 patients in the treatment group and 40 in the control group) were analyzed. Patients in the treatment group showed a lower weight than the control group (p <0.05), but there was no statistically significant difference between both groups for all the other factors. So we thought that demographic and baseline clinical characteristics were relatively balanced between the two groups (Table 1).

After nutrition intervention the incidence of nutritional risk was significantly lower among patients in treatment group (10.00 %), as compared to those before (100.00%) (p<0.05). While, the incidence of nutritional risk in control group showed no significant differences after the six months (92.50 %) and the baseline (100.00 %) (p >0.05). Meantime severe malnutrition and hypoproteinemia were observed less after nutrition intervention in treatment group than before (0.00 % vs. 37.50 %; 42.50 % vs.87.50 %, p <0.05). But hypoproteinemia was observed more after the six months in control group than before (85.00 % vs. 55.00 %, p <0.05) (Table 2). The proportion of patients with nutritional risk (NRS2002 ≥3) decreased from 100% to 10 % in the intervention group versus 100 % to 92.5 % in the control group (between group OR = 0.01, 95% CI: 0.00–0.05; d = 1.96, large effect). Severe malnutrition (PG SGA ≥9) was reduced from 37.5% to 0% in the intervention group, while it increased from 20% to 40% in controls (between group OR = 0.02, 95%CI: 0.00–0.18; d = 1.12, large effect).

In treatment group, Upper Arm Circumference, Tricep Skinfold Thickness, Calf Circumference, BMI and Muscle Metrics (MM) increased significantly after nutrition intervention (p <0.05), the control group also showed change about these indicators, however in the opposite case (p <0.05), the intervention group gained a mean of 4.20 kg (95%CI: 2.15, 6.25) more MM than the control group (d= 1.05, large effect). There were no significant difference in Fat Mass (FM), Percentage Body Fat (PBF) and Waist-to-hip Ratio (WHR) before and after the intervention in treatment group, but PBF and WHR were significantly higher after 6 months in control group (p <0.05). Body Cell Mass (BCM) and Phase Angle (PA) in treatment group were increased but in control group were decreased after 6 months (p <0.05). Total Protein, Albumin, Hemoglobin and Calcium in treatment group were higher after the intervention than before and in control group were lower than 6 months ago (p <0.05) (Table 3).

In treatment group, HGS increased significantly after exercise intervention (p <0.05), but in control group was a decrease (p <0.05), the between group mean difference was 4.10 kg (95% CI: 2.25, 5.95; d = 0.95, large effect). The 5XSTS scores decreased by 1.05s after exercise intervention in treatment group (p <0.05), but increase by 1.95s in control group (p <0.05). After exercise intervention the 6WT result showed that the walking speed increased by 0.15 m/s in treatment group but decreased by 0.2 m/s in control group after 6 months (p <0.05). The 6MWT result showed that after exercise intervention the walking distance increased by 50.58m in treatment group (p <0.05), while decrease by 32.00m in control group after 6 months (p <0.05) (Table 3), the intervention group improved by 73.43 m more than controls (95%CI: 45.20, 101.66; d = 1.18, large effect).

All enrolled patients showed good compliance with the intervention, and most completed the daily therapy as required. No obvious differences in adherence were observed with respect to age or tumor type. After psychology intervention HADS and PHQ-9 were decreased in treatment group, while were increased in control group after 6 months (p <0.05) (Table 3). HADS Total Score: The intervention group showed a greater reduction by a mean of 6.0 points (95%CI: 3.8, 8.2; d = 1.24, large effect). PHQ 9 Score: The between group mean difference was 4.5 points (95%CI: 2.9, 6.1; d = 1.08, large effect).

After 6 months, the physical function, role function, emotional function, social function and the overall health status score mean were significantly higher while the fatigue, nausea/vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial problems markedly decreased in treatment group (p <0.05) (Table 4). However, in control group the functional categories and the overall health status score mean were significantly lower while the fatigue, nausea/vomiting, pain, loss of appetite, constipation, and diarrhea markedly increased after 6 months (p <0.05) (Table 4). Other results were shown in Table 1.

All primary and secondary outcomes were further analyzed using ANCOVA with baseline weight and baseline values as covariates to account for the minor baseline imbalance in weight. After adjustment, all between-group differences remained statistically significant (all p <0.05), and the overall pattern of results was consistent with unadjusted analyses. These data confirmed that the baseline difference in weight did not influence the conclusions regarding the effectiveness of the combined nutrition, exercise, and psychological intervention.

DISCUSSION

The morbidity and mortality of malignant tumors are still extremely high and show an annual rising trend.[13,14] At present, there is no radical therapy for malignancy, surgery, radiotherapy and chemotherapy are still the mainstay of anti-tumor treatment in China.[15,16] Meanwhile, due to the long term anti-tumor treatment and tumor progression, the nutritional status and physical fitness gradually reduced, the mental health status and quality of life become worse, which are not conducive to recovery. In current oncologic rehabilitation is a major global concern that cannot be effectively tackled by any single therapy and intervention, so multidisciplinary approach of patients of malignancy is important and necessary. Therefore, the primary objective of this study is to investigate the rehabilitation outcome of patients by integrated nutrition, exercise and psychology intervention.

NRS2002 is a simple, powerful nutritional risk screening tool for patients, which is approved by the European Society of Parenteral and Enteral Nutrition (ESPEN) and the Chinese Society of Parenteral and Enteral Nutrition (CSPEN).[17,18] The PG-SGA is modified on the basis of Ottery's[19] Subjective Global Assessment (SGA), which is a specific assessment tool for the nutritional status of patients with malignancy.[20] Special medical formula (FSMP) has also been verified to improve nutritional status and sarcopenia in cancer patients at nutritional risk.[21] In this study, the intervention group showed striking improvements in nutritional status: NRS2002 nutritional risk decreased from 100% to 10%, and severe malnutrition (PG-SGA) fell from 37.5% to 0%. Although these changes appear large, they are credible and consistent with the intensive, multimodal intervention that included personalized nutrition support, dietary counseling, symptom management, and weekly monitoring. Furthermore, all outcomes were adjusted for baseline weight imbalance using ANCOVA, and the differences remained highly significant, confirming the validity of the findings. These data demonstrate that early, intensive nutritional intervention can effectively reverse nutritional risk and severe malnutrition in patients with malignancy. For elderly patients undergoing gastrointestinal cancer surgery, preoperative oral nutritional supplements also bring significant clinical benefits.[22]

In recent years, BIA has been gradually used for measurement and analysis of body composition in clinical practice due to its simplicity, non-invasiveness and high accuracy,[23] and it can accurately determine the body's water, fat and muscle content. PA is an important BIA-derived indicator, PA: Φ (°) = arctangent (XC / R) × (180 degrees / π),[24] it is an important indicator of cell membrane integrity and cell function.[25,26] Low PA is closely associated with poor prognosis in a variety of chronic diseases,[27,28] and with nutritional risk

and length of hospital stay in patients with malignancy.[29] Meantime, PA can also effectively evaluate the prognosis of patients, especially those with malignant tumors.[30-34] As shown by the results of the present study, the water content include Total Body Water (TBW), Intracellular Water (ICW) and Extracellular Water (ECW), muscle level and PA in treatment group were significantly increased after the combined interventions, but the opposite was true for the control subjects. The above results demonstrate that combined interventions can effectively improve patients' body composition, increase the patients' muscle level, and contribute to cell membrane integrity and function, whereas the administration of combined interventions do not significantly improve the fatty level. Meanwhile, it also be seen from the side that combined interventions are effective to improve patients nutritional status may be beneficial to improve patients' prognosis and quality of life.

HGS is a measure of overall muscular strength and it can predict adverse outcomes.[35] According to the European sarcopenia Consensus,[36] Asian Sarcopenia Consensus[37] and other international authoritative guidelines, HGS is one of the must-test items in the diagnosis of sarcopenia. The 6MWT is an inexpensive and feasible method to assessment muscular strength and be used as an indicator for evaluating the death or hospitalization.[38] The 6WT is a fast, reliable and sensitive measurement method to assessment muscular strength and can assess and monitor the functional status and overall health of the elderly population, the 6WT has been already considered to be the "sixth vital sign".[39] The 5XSTS is one of the valid indicators for the lower limb function40 and used to assess physical function.[37] The results from this study showed that the HGS and the 6-minute walk distance were increased significantly, the 6-m walking time and the 5XSTS consumption were decreased significantly in treatment group after combined interventions. This suggests that combined interventions improved muscle strength, and may be beneficial to improve patients' prognosis and quality of life.

Patients with malignancy not only suffer from physical pain, but also various psychological problems, such as depression, anxiety, fear and despair. These negative emotions will not only reduce the quality of life of patients, but seriously affect the treatment effect.[41-43] However, whether psychological intervention can play a positive role in the psychological status of patients with malignancy, and whether it is necessary to apply to clinical treatment is still controversial.[44] Different scales and questionnaires can be used to measure and evaluate anxiety and depression, such an the HADS[45,46] and PHQ-9.[47,48] Results from this study demonstrate HADS scores and PHQ-9 scores in treatment group were decreased after combined interventions and in control group were increased after 6-month. Considering the

results of this study, combined interventions have an important role in decreasing of anxiety and depression in patients with malignancy, which in turn promotes the rehabilitation of patients.

A consensus has been reached by modern cancer science that quality of life is also an important indicator reflecting the treatment effect and rehabilitation status of cancer patients besides survival rate, mortality rate and other indicators.49 We evaluated quality of life using the standardized QLQ-C30 (version 3). It showed that after combined interventions, the values from the functional category and for the overall health status of patients in treatment group were increased, and the symptoms category scores mean decreased, while the opposite was true for the control group. To sum up, the present study indicates that when patients received anti-tumor therapy and disease progression their quality of life become worse, however, This trend can to be reversed by combined interventions.

Notably, patients in the control group exhibited a trend toward deterioration across nearly all outcome domains over the study period. This observation is clinically plausible in the setting of advanced cancer, as disease progression is frequently accompanied by gradual declines in physical performance, emotional well-being, and overall quality of life in the absence of targeted supportive interventions.

There are limitations to the research. First, the present study was open label, and the same investigators performed both intervention delivery and outcome assessments, which may lead to performance bias and assessment bias, particularly for subjective outcomes including nutritional scores, patient reported symptoms, and quality of life. Although standardized protocols were used to reduce bias, this issue should be considered when interpreting the results. Second, baseline weight imbalance existed between-groups; although ANCOVA was applied for adjustment, confounding effects cannot be completely excluded. Third, the single center design may limit the generalizability of the findings.

In summary, the combined intervention encompassing nutrition, exercise, and psychological support effectively improved the nutritional status and physical quality, relieve the anxiety and depression, and improve the quality of life of patients with Malignancy. And combined interventions maybe enhance their tolerance of anti-tumor therapy and promote the rehabilitation. Finally, the results of this study lay a foundation for the clinical promotion of combined interventions model for patients with malignancy in the future.

This study was conducted at a single center, which may limit the generalizability of the findings to broader outpatient or community oncology populations.Nevertheless, the present results provide preliminary but promising evidence for the efficacy of the intervention, and

further investigation in a larger, properly powered multicentre study is warranted to confirm these observations.

Conclusion

The combined interventions, encompassing nutrition, exercise, and psychological support，can effectively improve the nutritional status and physical quality, relieve the anxiety and depression, and improve the quality of life of patients with Malignancy. And combined interventions maybe can enhance their tolerance of anti-tumor therapy and promote the rehabilitation.

SUPPLEMENTARY MATERIALS

All supplementary tables and figures are available upon request from the editorial office, and are also accessible on the journal's webpage (apjcn.qdu.edu.cn).

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CONFLICT OF INTEREST AND FUNDING DISCLOSURE

The authors declare no conflict of interest related to this work.

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Table 1. Patients' demographic and baseline characteristics

Characteristic	TG (n = 40)	CG (n = 40)	z/t/χ^2	*p*
Age, years	58.5 (19.8)	59.0 (12.8)	-0.443	0.658
≤60	22 (55.0 %)	21 (52.5 %)		
>60	18 (45.0 %)	19 (47.5 %)	0.050	0.823
Sex				
Man	19 (47.5 %)	19 (47.5 %)		
Woman	21 (52.5 %)	21 (52.5 %)	0.000	1.000
Weight, kg	61.5 ± 11.9	67.1 ± 10.5	-2.25	0.028
Primary tumor site				
Tumor of the respiratory system	9 (22.5 %)	16(40.0 %)		
Tumor of the digestive system	19 (47.5 %)	13(32.5 %)		
Tumor of the genital system	4 (10.0 %)	2(5.00 %)		
Tumor of the other system	8 (20.0 %)	9(22.5 %)	3.81	0.283
Tumor stage (TNM)				
II	8 (20.0 %)	10 (25.0 %)		
III	9 (22.5 %)	11 (27.5 %)		
IV	23 (57.5 %)	19 (47.5 %)	0.803	0.669
Modality of treatment				
Radiotherapy	9 (22.5 %)	10 (25.0 %)		
Chemotherapy	27 (67.5 %)	19 (47.5 %)		
Symptomatic treatment	4 (10.0 %)	11 (27.5 %)	4.71	0.095
Comorbid chronic disease				
With	4 (10.0 %)	8 (20.0 %)		
Without	36 (90.0 %)	32 (80.0 %)	1.57	0.210

TG, treatment group; CG, control group
Data presented as mean ± standard deviation or M (Q) or n (%).

Table 2. Patients' nutritional status in two groups

	TG				CG			
	Before	After	χ^2	*p*	Before	After	χ^2	*p*
NRS2002, score								
<3	0 (0.00)	36 (90.0)			0 (0.00)	3 (7.50)		
≥3	40 (100)	4 (10.0)	65.5	<0.001	40 (100)	37 (92.5)	1.39	0.239
PG-SGA, score								
0-1	0 (0.00)	9 (22.5)			1 (2.50)	2 (5.00)		
2-8	25 (62.5)	31 (77.5)			31 (77.5)	22 (55.0)		
≥9	15 (37.5)	0 (0.00)	33.9	<0.001	8 (20.0)	16 (40.0)	4.59	0.101
Albumin, g/L								
<40	35 (87.5)	17 (42.5)			22 (55.0)	34 (85.0)		
≥40	5 (12.5)	23 (57.5)	17.8	<0.001	18 (45.0)	6 (15.0)	8.57	0.003

TG, treatment group; CG, control group
Data presented as n (%).

Table 3. Patients' nutrition, exercise and psychology indicators in two groups

	TG				CG			
	Before	After	z/t	*p*	Before	After	z/t	*p*
Upper arm circumference, cm	24.3 ± 3.50	25.3 ± 3.53	-5.20	<0.001	27.3 ± 4.65	26.6 ± 5.20	-4.15	<0.001
Tricep skinfold thickness, mm	9.50 (9.25)	11.5 (10.0)	-5.10	<0.001	11.0 (8.00)	10.5 (8.50)	-3.62	<0.001
Calf circumference, cm	32.9 ± 3.46	34.1 ± 3.38	-9.11	<0.001	34.1 ± 5.25	33.4 ± 5.33	-4.47	<0.001
Weight, kg	61.4 ± 11.9	64.1 ± 12.0	-4.96	<0.001	67.1 ± 10.5	65.1 ± 10.2	-4.43	<0.001
BMI, kg/m^2	23.6 ± 3.34	24.6 ± 3.35	-4.93	<0.001	25.8 ± 4.85	25.2 ± 3.46	-4.27	<0.001
Muscle mass, kg	37.7 (12.6)	40.1 (12.3)	-5.08	<0.001	42.5 ± 7.03	39.9 ± 7.19	-5.06	<0.001
Skeletal muscle mass, kg	21.1 (8.06)	23.1 (8.13)	-5.03	<0.001	24.3 ± 4.39	23.0 ± 4.33	-4.97	<0.001
Appendicular skeletal muscle mass index, kg/m^2	6.60 ± 0.99	6.98 ± 0.85	-4.50	<0.001	7.02 ± 0.96	6.68 ± 0.96	-4.52	<0.001
Basal metabolic rate, kcal	1236 (287)	1290 (293)	-5.08	<0.001	1321 (261)	1262 (275)	-5.11	<0.001
Fat mass, kg	17.9 (9.38)	18.2 (9.82)	-0.202	0.840	21.7 (5.88)	21.2 (8.66)	-0.80	0.424
Percentage body fat, %	31.2 ± 9.00	29.2 ± 9.11	-1.20	0.232	32.2 ± 8.10	33.8 ± 8.33	-3.14	0.002
Waist-to-hip ratio	0.90 (0.11)	0.89 (0.08)	-0.060	0.952	0.90 (0.09)	0.94 (0.10)	-2.21	0.027
Body cell mass, kg	26.9 ± 5.41	28.6 ± 5.97	-4.54	<0.001	28.9 ± 4.83	27.5 ± 4.75	-4.99	<0.001
Phase angle, degree	5.32 ± 0.75	5.72 ± 0.70	-3.95	<0.001	5.60 (1.05)	4.95 (1.60)	-4.94	<0.001
Hand grip strength, kg	20.3 (12.60)	22.9 (12.5)	-4.56	<0.001	24.0 (9.20)	19.8 (7.73)	-5.01	<0.001
5XSTS, s	12.1 (5.15)	11.1 (4.65)	-4.56	<0.001	10.3 (3.57)	12.3 (4.80)	-4.42	<0.001
6WT, m/s	0.93 ± 0.26	1.08 ± 0.30	-3.44	<0.001	1.10 (0.20)	0.90 (0.28)	-4.95	<0.001
6MWT, m	388 ± 93.4	439 ± 79.3	-4.72	<0.001	422 (86.5)	391 (97.3)	-5.07	<0.001
HADS	4.50 (6.75)	1.00 (3.75)	-4.76	<0.001	3.50 (6.75)	6.00 (8.25)	-4.22	<0.001
PHQ-9	4.00 (6.00)	1.50 (3.00)	-4.47	<0.001	2.00 (4.00)	4.00 (3.75)	-4.49	<0.001
NLR	1.02 (2.29)	0.92 (4.21)	-1.59	0.113	1.03 (3.33)	0.73 (6.45)	-2.07	0.038
PLR	100 (213)	73.3 (153)	-1.99	0.047	49.7 (300)	32.4 (234)	-2.45	0.014
Total protein, g/L	60.8 ± 6.72	68.8 ± 6.44	-11.0	<0.001	63.7 ± 6.07	62.2 ± 5.38	-3.78	<0.001
Albumin, g/L	36.3 ± 3.89	40.5 ± 4.08	-9.48	<0.001	39.6 ± 3.69	36.7 ± 5.55	-4.56	<0.001
Hemoglobin, g/L	110 ± 16.2	122 ± 16.8	-8.39	<0.001	125 ± 16.2	120 ± 17.3	-3.09	0.002
Calcium, mmol/l	2.23 (0.11)	2.31 (0.17)	-5.31	<0.001	2.32 (0.19)	2.21 (0.12)	-4.20	<0.001

TG, treatment group; CG, control group; 5XSTS, five-times sit-to-stand test; 6WT, 6-metre walking test; 6MWT, 6-minute walk test; HADS, Hospital Anxiety and Depression Scale; PHQ-9, Patient Health Questionnaire 9; NLR, Neutrophil-to-lymphocyte ratio; PLR, Platelet-to-lymphocyte ratio..
Data presented as mean ± standard deviation or M (Q).

Table 4. Patients quality of life in two groups

	TG				CG			
	Before	After	z/t	*p*	Before	After	z/t	*p*
Physical functioning	73.3 (13.3)	86.7 (18.3)	-5.38	<0.001	73.3 (13.3)	66.7 (13.3)	-2.43	0.015
Role functioning	66.7 (16.7)	83.3 (33.3)	-3.02	0.003	66.7 (33.3)	50.0 (33.3)	-2.14	0.032
Emotional functioning	66.7 (31.3)	83.3 (29.2)	-2.15	0.031	75.0 (33.3)	66.7 (8.33)	-2.56	0.010
Cognitive functioning	83.3 (16.7)	83.3 (33.3)	-1.08	0.280	83.3 (29.2)	66.7 (33.3)	-2.38	0.017
Social functioning	66.7 (16.7)	83.3 (33.3)	-3.67	<0.001	66.7 (25.0)	50.0 (33.3)	-3.00	0.003
Global QOL	66.7 (16.7)	75.0 (16.7)	-3.72	<0.001	66.7 (16.7)	41.7 (25.0)	-2.93	0.003
Fatigue	33.3 (11.1)	22.2 (22.2)	-2.90	0.004	33.3 (11.1)	55.6 (30.6)	-2.72	0.007
Nausea/vomiting	50.3 (33.3)	16.7 (29.2)	-3.30	<0.001	50.3 (33.3)	66.7 (16.7)	-3.20	0.001
Pain	33.3 (0.00)	16.7 (33.3)	-3.11	0.002	33.3 (16.7)	50.0 (16.7)	-4.02	<0.001
Dyspnea	33.3 (0.00)	0.00 (33.3)	-3.86	<0.001	33.3 (25.0)	33.3 (33.3)	-1.94	0.052
Insomnia	33.3 (33.3)	0.00 (33.3)	-3.46	0.001	33.3 (0.00)	33.3 (33.3)	-1.54	0.124
Appetite loss	33.3 (33.3)	0.00 (33.3)	-3.61	<0.001	33.3 (33.3)	66.7 (33.3)	-2.28	0.023
Constipation	33.3 (25.0)	0.00 (33.3)	-2.65	0.008	33.3 (0.00)	50.0 (33.3)	-3.29	0.001
Diarrhea	33.3 (66.7)	0.00 (33.3)	-2.05	0.040	33.3 (33.3)	66.7 (33.3)	-4.14	<0.001
Financial problems	66.7 (33.3)	33.3 (33.3)	-4.99	<0.001	66.7 (58.3)	66.7 (33.3)	-1.19	0.234

TG, treatment group; CG, control group.
Data presented as M (Q).

Table 5. Comparison of other indicators in two groups

	TG				CG			
	Before	After	z/t	*p*	Before	After	z/t	*p*
Intracellular water (L)	17.7 (6.18)	18.9 (6.30)	-5.03	<0.001	20.2 ± 3.37	19.2 ± 3.32	-4.99	<0.001
Extracellular water (L)	11.6 (3.98)	12.2 (3.81)	-4.34	<0.001	13.1 ± 2.16	12.4 ± 2.05	-5.09	<0.001
Total body water (L)	29.6 (9.83)	31.0 (9.59)	-5.09	<0.001	33.2 ± 5.50	31.4 ± 5.26	-5.09	<0.001
Protein (kg)	7.64 (2.67)	8.17 (2.74)	-5.01	<0.001	8.71 ± 1.46	8.29 ± 1.44	-4.99	<0.001
Mineral (kg)	2.75 (0.87)	3.10 (0.85)	-4.68	<0.001	3.12 (0.72)	2.93 (0.63)	-4.53	<0.001
Fat free mass (kg)	40.1 (13.3)	42.6 (13.6)	-5.05	<0.001	45.0 ± 7.40	42.9 ± 7.20	-5.11	<0.001
Upper arm muscle circumference (cm)	23.9 ± 2.34	24.4 ± 2.50	-4.35	<0.001	25.4 ± 2.33	25.0 ± 2.29	-2.13	0.033
Muscle mass of right arm (kg)	2.14 (1.11)	2.31 (0.99)	-4.10	<0.001	2.52 ± 0.62	2.35 ± 0.56	-4.13	<0.001
Muscle mass of left arm (kg)	2.12 (0.98)	2.28 (0.87)	-3.64	<0.001	2.47 ± 0.58	2.33 ± 0.54	-3.95	<0.001
Muscle mass of trunk (kg)	19.2 ± 3.80	20.1 ± 3.93	-4.27	<0.001	20.8 ± 3.60	20.1 ± 3.31	-3.96	<0.001
Muscle mass of right leg (kg)	6.22 (2.46)	6.62 (2.42)	-3.78	<0.001	6.65 ± 1.36	6.36 ± 1.32	-3.87	<0.001
Muscle mass of left leg (kg)	6.05 (2.44)	6.63 (2.30)	-5.19	<0.001	6.66 ± 1.35	6.37 ± 1.35	-4.17	<0.001
Dropsy index	0.39 (0.01)	0.40 (0.01)	-0.378	0.706	0.39 ± 0.01	0.39 (0.01)	-0.51	0.613
Visceral fat area (cm^2)	84.8 (61.4)	86.1 (64.7)	-0.081	0.936	105 (48.4)	112 (58.7)	-1.56	0.119
White blood cells (10^9/L)	3.83 ± 1.28	4.98 ± 1.56	-4.56	<0.001	4.90 (3.08)	3.85 (2.05)	-4.40	<0.001
Neutrophils (10^9/L)	2.28 (1.39)	2.95 (1.76)	-3.62	<0.001	3.20 (2.73)	2.45 (1.78)	-3.73	<0.001
Lymphocyte(10^9/L)	2.05 (27.1)	1.65 (25.6)	-0.65	0.519	4.95 (26.9)	5.80 (29.0)	-0.49	0.624
Platelets (10^9/L)	204 ± 67.9	165 ± 53.6	4.91	<0.001	206 ± 69.7	172 ± 56.8	-4.39	<0.001
Alanine aminotransferase (U/L)	20.8 (19.9)	19.2 (16.8)	-1.06	0.290	16.8 (16.7)	18.0 (15.1)	-0.29	0.773
Aspartate aminotransferase (U/L)	22.9 (13.1)	21.9 (12.2)	-0.397	0.692	20.9 (13.8)	22.1 (15.1)	-0.968	0.333
C-reactive protein (mg/L)	3.47 (8.29)	1.96 (2.06)	-3.55	<0.001	2.03 (5.13)	3.94 (8.10)	-3.03	0.002
Blood urea nitrogen (mg/dL)	4.70 (2.12)	4.80 (1.96)	-2.37	0.018	4.78 (1.56)	4.65 (2.05)	-0.430	0.667
creatinine (μmol/L)	59.1 (20.3)	56.8 (22.5)	-0.98	0.334	56.8 (17.8)	57.0 (20.3)	-0.444	0.657
Blood glucose (mmol/L)	4.84 (0.86)	4.75 (0.89)	-0.174	0.862	5.32 (1.58)	5.08 (1.60)	-0.600	0.548
Potassium (mmol/L)	3.93 ± 0.33	4.09 ± 0.35	-2.62	0.013	4.10 ± 0.40	3.96 ± 0.39	-2.55	0.011
Sodium (mmol/L)	140 (2.75)	141 (3.00)	-2.67	0.008	140 (3.00)	140 (3.00)	-0.611	0.541

TG, treatment group; CG, control group
Data presented as mean ± standard deviation or M (Q).

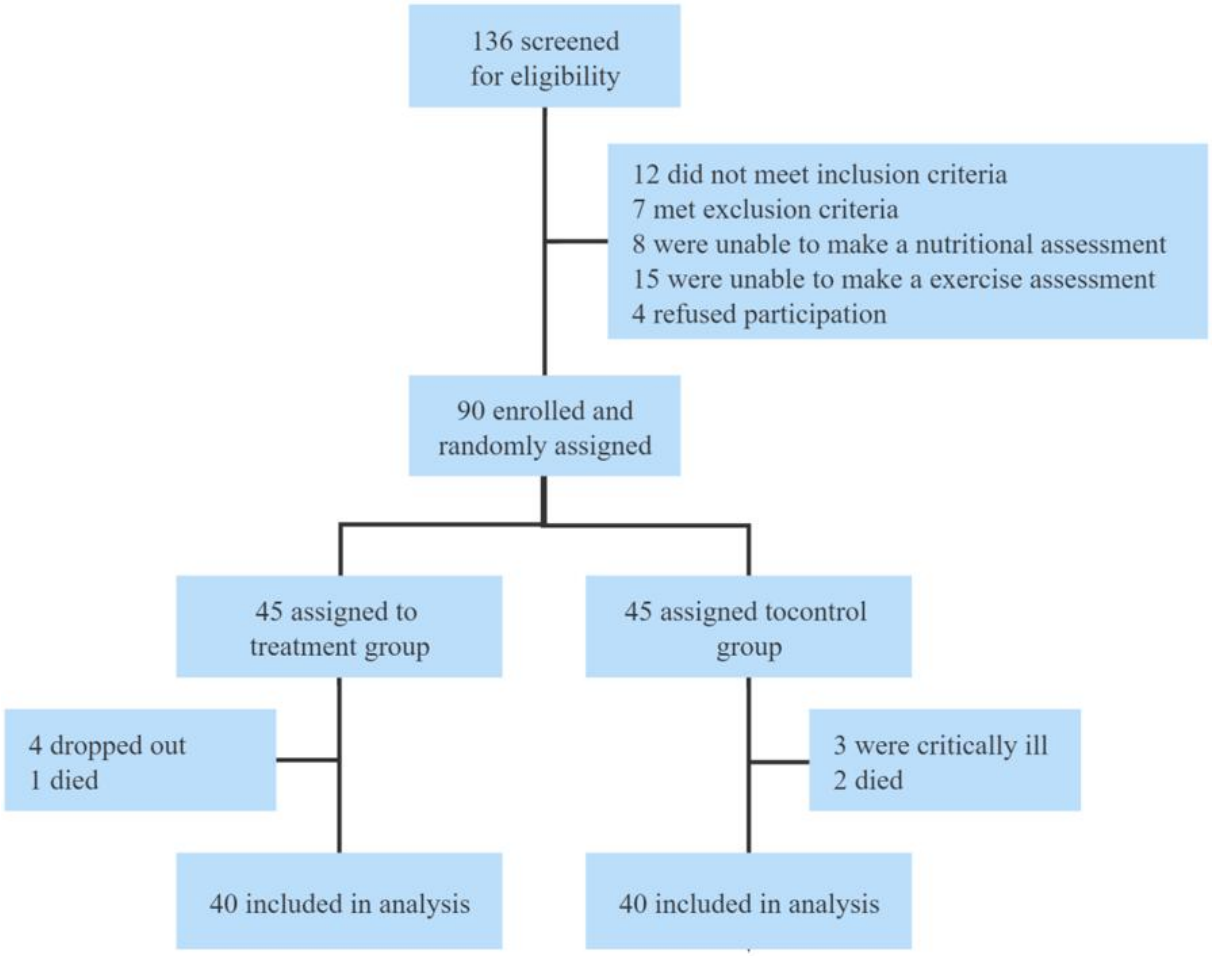

Figure 1. Trial profile

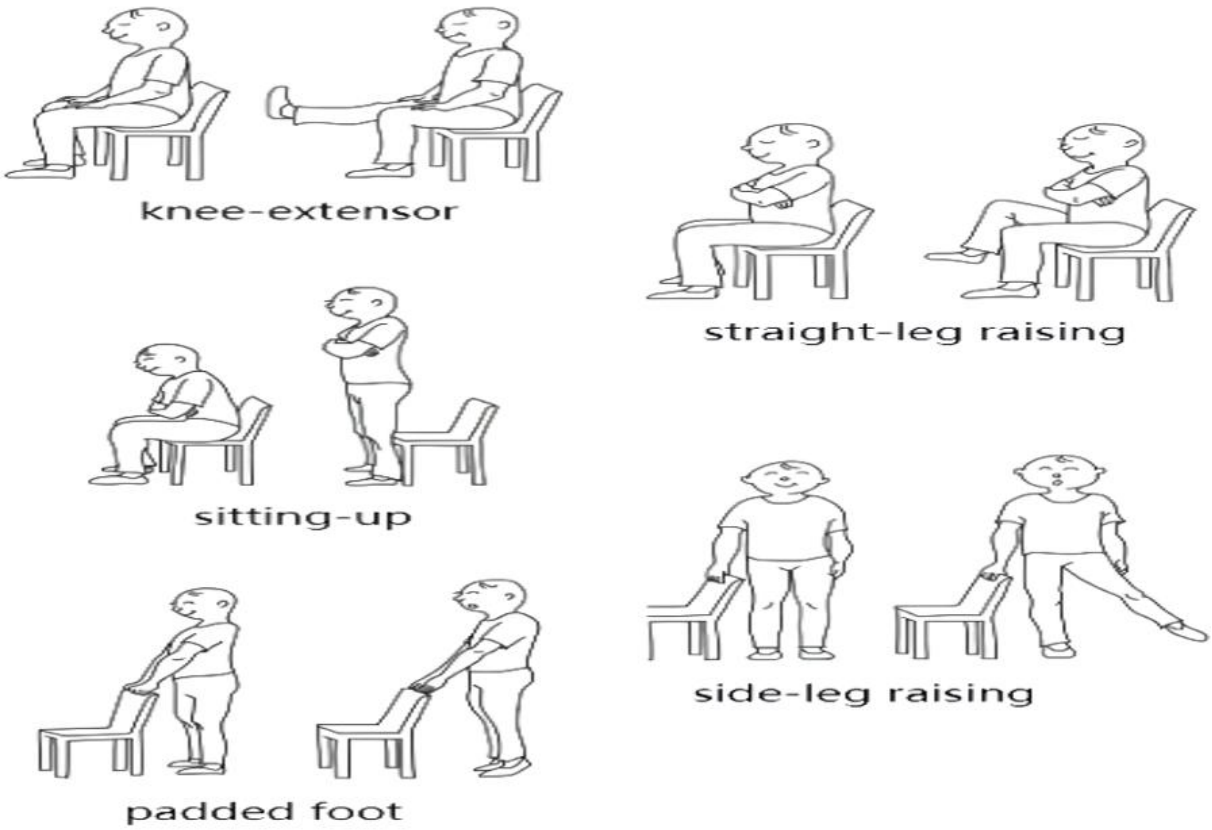

Figure 2. Multiple exercise modalities