Original Article

Effects of FSMP on nutrition status and sarcopenia among nutritional risk cancer patients: A randomized, double-blind, placebo-controlled study

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Background and Objectives: Cancer patients at nutritional risk have a worse prognosis, but this can be improved by nutritional support. Food for special medical purposes (FSMP), as a new form of nutritional support, needs to be further evaluated for its safety and efficacy in these patients. Our study elucidate the impact of FSMP on nutritional status and sarcopenia among nutritional risk cancer outpatients by assessing the NRS2002 score, exercise performance, muscle mass, and inflammatory factors pre- and postintervention. **Methods and Study Design:** We conducted a single-centre, double-blind, randomized controlled interventional study. Patients from the oncology clinic with nutritional risk were randomly allocated to the control group or the FSMP group and received oral intervention for 8 weeks. The primary outcome was improvement in nutritional risk, while the secondary outcomes were improvements in sarcopenia prevalence and physical performance indicators. Other outcomes included alterations in calf circumference, hsCRP, 25(OH)VD3, Alb. etc. A linear mixed-effects model was used to compare the prepost-intervention changes in these results. **Results:** Thirty-six cancer patients were included, 25 completed the study. The percentage of patients at nutritional risk after intervention in the FSMP group was significantly lower than the control group (X^2=4.186, p=0.041). The FSMP group demonstrated significant improvements in the TUG test, gait speed, grip strength, and upper-limb muscle mass. However, there was no significant improvement in the rate of sarcopenia. Moreover, calf circumference, hsCRP, 25(OH)VD3, Alb exhibited no significant changes. **Conclusions:** FSMP can effectively improve the nutritional status, physical performance and upper-limb muscle mass of cancer patients.

Key Words: FSMP, nutritional risk, sarcopenia, cancer patient, RCT

INTRODUCTION

Inpatients and outpatients frequently suffer from nutritional risk and malnutrition.[1] A large-scale, multicentre survey of nutritional risk, malnutrition, and nutritional support (NUSOC) led by the Chinese Medical Association's Parenteral and Enteral Nutrition Branch (CSPEN) across hospitals of various sizes in the eastern, central, and western regions of China revealed that the average prevalence of nutritional risk among basic surgery, thoracic surgery, gastroenterology, respiratory medicine, neurology, and nephrology inpatients was as high as 35%. Among patients experiencing nutritional risk/ malnutrition, only 33% have received nutritional support treatment.[2] There is widespread research on individuals who experience "nutritional risk without adequate nutrition".[3] Extensive clinical research evidence suggests that nutritional risk and malnutrition can lead to the deterioration of patients' nutritional status and adverse clinical outcomes, including an increase in the risk of nutrition-related complications, longer hospital stays, higher hospital costs, a higher cost-effectiveness ratio (C/E ratio), higher readmission rates, a diminished quality of life, and higher all-cause mortality rates.[4] Our team demonstrated that nutritional support treatment for patients at nutritional risk can effectively improve their nutritional status, reduce the incidence rates of infectious complications and overall complications,[5-7] and enhance the C/E ratio, among other benefits.[8]

Sarcopenia is a medical and economic issue that is becoming more prevalent in our ageing society. The The prevalence of sarcopenia in individuals aged 70 and older is approximately 20%,[9] and the prevalence is 50% in those aged 80 and above. Patients with sarcopenia have higher rates of complications and mortality.[10] The occurrence of sarcopenia is believed to be the result of multiple contributing factors.[11] One of the factors is lack of exercise, whether it is due to a sedentary lifestyle or

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immobility related to illness or disability.[12] Sarcopenia is also associated with malnutrition, regardless of whether it is a result of low dietary intake (starvation, inability to eat), reduced nutritional bioavailability (diarrhoea, vomiting), or increased nutritional demands (cancer or organ failure associated with cachexia).[13, 14] Low muscle mass has recently been proposed as part of the definition of malnutrition.[15]

In recent years, food for special medical purposes (FSMP) has become an essential component of clinical nutritional support, addressing the specialized dietary needs of patients with medical conditions such as chemotherapy-induced anorexia in cancer patients, premature infants, and metabolic disorders. FSMP encompasses three categories: complete nutritional formulas, disease-specific formulas, and modular nutrient components. For oncology patients, FSMP provides high-protein, micronutrient-rich formulations that may improve energy intake and mitigate muscle loss. Localized production tailored to regional dietary preferences enhances patient compliance. While several complete nutritional formulas have obtained regulatory approvals in China, their clinical safety and efficacy require further validation.

Nutritional risk, quantified by the NRS2002 score, reflects the severity of energy-protein deficits in cancer patients. Concurrently, sarcopenia—assessed via timed up-and-go (TUG), grip strength, and muscle mass—is a common complication of malnutrition, with both factors significantly impacting clinical outcomes. This study, through a randomized controlled design, investigates the effects of FSMP on the nutritional status, sarcopenia, and functional indicators of cancer patients with nutritional risk, aiming to provide evidence-based support for clinical nutrition therapy.

METHODS

Study design

This was a single-centre (Peking Union Medical College Hospital), double-blind, randomized controlled clinical trial with an 8-week intervention (from February 2022 to August 2022). The study protocol was approved by the Ethics Review Committee of Peking Union Medical College Hospital (Ethics No. HS-3259) and registered in the National Medical Research Registration Information System of the National Health Security Platform (Registration No. MR-11-22-012418), and the study was publicly released after passing the review process. All interventions and clinical evaluations strictly adhered to the provisions of the Declaration of Helsinki in 1995 (as revised in Edinburgh 2000).

Randomization

Both the test and placebo formulations were produced by the manufacturer, packaged directly in identical packaging, randomized and numbered and stored in a temperature-controlled warehouse. After obtaining informed consent from the patients, the formulations were randomly shipped, and box numbers were recorded. Allocation concealment was achieved through independent packaging, third-party warehouse management, and blinded numbering, ensuring that both researchers and participants were unaware of the group assignments during the intervention period. After the final follow-up, externally hired statisticians obtained group information for analysis. If severe illness or complications arose during the study, the process was halted, the Ethics Committee was notified, and unblinding occurred under surveillance to assess the impact of the formulation on adverse events.

Inclusion and exclusion criteria

The study involved cancer patients from Peking Union Medical College Hospital's Oncology Department. Participants recruited via posters were evaluated using the Nutritional Risk Screening 2002 (NRS2002) with inclusion requiring a score of ≥3. The exclusion criteria included severe cognitive impairment; abnormal renal function as indicated by endogenous creatinine clearance <30 ml/min (calculated by the Cockcroft-Gault formula based on fasting blood creatinine); abnormal liver function as demonstrated by total bilirubin >34 μmol/L or alanine aminotransferase >80 U/L; recent enteral nutrition support therapy; who are unable to cooperate in completing nutritional assessments (such as physical function tests), oral nutritional supplementation; adherence to a high-energy or high-protein diet (within the three months preceding the study); and consumption of calcium supplements (exceeding 500 mg per day), vitamin D supplements (over 10 μg/400 IU per day), or protein/amino acid supplements.

Nutritional intervention

The intervention group received an FSMP formulation (per 100 g: 1832 kJ, protein: 16.2 g, fat: 13.4 g, carbohydrates: 62.0 g, with DHA, EPA, levocarnitine, taurine, and various vitamins and trace elements; formulation details are provided in Supplementary Table 1). The control group received a flavoured isocaloric placebo (per 100 g: 1812 kJ, protein: 1.2 g, fat: 15.4 g, carbohydrates: 82.0 g; formulation details are provided in Supplementary Table 2). Patients were instructed to consume 30g thrice daily, ingesting FSMP/placebo between meals. Intake was monitored through the distribution of pre-portioned packages and daily intake logs. Both groups received standardized dietary recommendations, and their dietary intakes were recorded during monthly follow-ups. Monthly face-to-face or telephonic consultations for nutrition counselling included reviewing diet records, assessing adherence, and answering questions. The FSMP and the isocaloric placebo utilized in this study were produced by Zhejiang Hai zheng Su Li kang Biotechnology Co., Ltd.

Nutritional assessment

In addition to collecting demographic data (age and sex) and general medical history (primary admission diagnosis, number of comorbidities, and medications), the following data were evaluated:

NRS2002 score

The NRS2002 score was assessed and recorded before and after participation. An NRS2002 score <3 at the follow-up visit was considered to indicate nutritional improvement.

Weight and body mass index (BMI): Patients' weight (to the nearest 0.1 kg) and height (to the nearest 0.5 cm) were measured in the morning on an empty stomach ac-

cording to standard procedures, and BMI was calculated based on these measurements.

Sarcopenia assessment

The diagnosis of sarcopenia was conducted in accordance with the AWGS2019 and EWGSOP2 criteria, as shown in Table 1.[16, 17]

Body composition analysis

Bioelectrical impedance analysis (BIA) was performed using an HKey350 BIA device (Siemens) to assess body composition in fasted patients.

Physical function evaluation

Gait speed was gauged using a 4-metre walk test in a 10-metre corridor. Patients accelerated for 3 metres, maintained speed for the next 4 metres (the "test" zone), and decelerated over the final 3 metres. The fastest of two-timed trials, from 0 to 4 metres, was recorded. Assistive devices were allowed if necessary. The timed up-and-go (TUG) test quantifies the duration patients require to stand from an armless chair, traverse 3 metres, pivot, return, and reseat themselves. The shortest time across three trials was documented.

Grip strength

Grip strength was measured using a hydraulic hand dynamometer (Xiang Shan), with patients standing and their arms vertical. They gripped the device thrice with maximum force; the highest value in kg was recorded. Lower-limb muscle status was assessed by measuring calf circumference at its thickest part, with the patient sitting and calves at a right angle to the thighs. Three measurements were taken and averaged. If deep venous thrombosis or swelling exceeding grade 2 was present, the affected side's measurement was discarded. The average bilateral calf circumference in cm was reported for further analysis.

Serum evaluation

Fasting venous blood samples were collected to assess the following parameters: complete blood cell count, glucose, ALT, albumin, prealbumin, creatinine, blood urea nitrogen, serum electrolytes, transferrin, total cholesterol, high-sensitivity C-reactive protein (hsCRP) and 25(OH)VD3 levels. Inflammatory markers (IL-6, IL-8, IL-10, TNF-α) and TB lymphocyte subgroups were also analysed.

Outcome measures

The primary outcome was the improvement in the NRS2002 score after 8 weeks of intervention. The key secondary outcomes were improvements in sarcopenia prevalence, TUG and gait speed, grip strength and muscle mass assessed by BIA. Other secondary outcomes included changes in calf circumference; serum 25-OH-VD3, hsCRP, albumin and prealbumin levels; inflammatory factors; and T-cell subsets.

Adverse events

Patients were actively monitored to detect any potential gastrointestinal side effects related to the consumption of the nutritional intervention formula (common adverse events). The occurrence of any unexpected serious adverse events was also recorded. If the research team determined that there was a formulation-related risk, it was reported to the ethics committee for evaluation, and unblinding was performed if necessary.

Sample size calculation and statistical analysis

In the absence of preliminary data to estimate the expected treatment difference, based on the two-independent samples t-test, we set the effect size (Cohen's $d = 0.5$), $\alpha = 0.05$, and $\beta = 0.2$, and applied the sample size calculation" formula to determine the sample size. n=([2(Z_(α/2)+Z_β)]^2×σ^2)/d^2. A sample size of 30 patients (15 per group) was used To account for a 10% dropout rate per group, 34 patients were randomly allocated to each group (17 per treatment group).

The efficacy analysis included patients who achieved the primary outcome and completed the first follow-up. Supportive analyses were conducted for primary and key secondary outcomes. Continuous variables are represented as the means and SDs. Chi-square tests were used to assess improvements in nutritional risk and sarcopenia between groups. The secondary outcomes, which were continuous values, were evaluated by the Kolmogorov–Smirnov test to determine whether they were normally distributed. Then, these normally distributed secondary outcomes were evaluated by a linear mixed-effects model (LMM) and reported as the difference in the marginal means of the two groups post- and preintervention. The

Table 1. Diagnostic criteria for sarcopenia

	EWGSOP2		AWGS2019	
	Men	Women	Men	Women
Muscle mass (BIA)	SMI <7.0 kg/m^2	SMI <5.5 kg/m^2	SMI <7.0 kg/m^2	SMI <5.7 kg/m^2
Grip strength	<27 kg	<16 kg	<28 kg	<18 kg
Gait speed	<0.8 m/s		<1 m/s	
Pre-sarcopenia	low grip strength		-	
Sarcopenia	Low grip strength + low muscle mass		Low muscle mass + low grip strength or low gait speed	
Severe sarcopenia	Low grip strength + low muscle mass + low gait speed		Low grip strength + low muscle mass + low gait speed	

AWGS2019: Asian Working Group for Sarcopenia: 2019 Consensus, BIA: bioelectrical impedance analysis, EWGSOP2: European Working Group on Sarcopenia in Older People 2nd Consensus.

model includes the factors treatment group (FSMP, control) and sex as fixed effects. Other covariates considered to be fixed effects included the values of each outcome index at baseline. Patient-specific effects with a normal distribution were entered into the model as random effects. The unstructured covariance matrix was used for the residuals. Pearson's correlation analysis was used to evaluate relationships among outcomes after adjusting for control variables, represented by the PCC. Analyses were performed using IBM SPSS Statistics version 21.0.0 and SAS version 9.4 (SAS Institute), with a two-sided p value < 0.05 indicating statistical significance.

RESULTS

Study population demographics

From the study's commencement on February 24, 2022, 36 subjects consented and completed the initial evaluation. Of these, exclusions occurred due to abnormal liver function 2, personal withdrawals 2, deaths during the study 5, and loss to follow-up 2, leaving 25 patients who completed follow-up. The cancer types of these patients comprised lung cancer (24%), gastrointestinal malignancies (36%), breast cancer (32%), and others (8%). However, due to the small sample size (n=25), subgroup analysis may result in insufficient statistical power. After unblinding, 17 patients were in the FSMP group, and 8 were in the control group. The study's progression is depicted in the flowchart in Figure 1.

The demographic details of the patients are compiled in Table 2. All the subjects were nutritionally at risk, with an average NRS2002 score of 3.4±0.5. The safety and tolerability of the intervention in both groups were satisfactory, with no instances of abdominal discomfort, diarrhoea, nausea, vomiting, or other intolerable symptoms related to the interventions. Some subjects encountered minor difficulty in dissolving the intervention formulation, necessitating additional stirring. Two subjects expressed distaste for the intervention formulation but managed to tolerate it.

Primary outcome

The chi-square test for the remediation rate of disparate intervention methods revealed a significant difference in nutritional risk improvement between the FSMP and control groups (χ^2=4.186, two-tailed p value of 0.041), signifying that FSMP is more efficacious at ameliorating nutritional risk than the placebo, as shown in Table 3.

Sarcopenia: Using two diagnostic methods, it was found that FSMP intervention did not significantly improve sarcopenia compared to the isocaloric placebo.

Secondary outcomes

The secondary outcomes were as follows: post- and pre-intervention differences between the FSMP and control groups were evaluated by the LMM. In terms of physical function and muscle mass, we found that the FSMP group exhibited significant reductions in TUG time and enhancements in gait speed, grip strength, and upper-limb and trunk muscle mass. However, no differences were detected in calf circumference or lower-limb muscle mass. On the other hand, in terms of the levels of nutrition-related serum markers and inflammatory markers, there were no significant differences in the levels of albumin, prealbumin, or hs-CRP between the two groups

Table 2. Demographics of the study population

	FSMP	Control	p
Male (total)	9 (17)	3 (8)	0.49
Height (cm)	167.4±6.8	168.0±10.1	0.87
Weight (kg)	57.0±9.1	58.3±9.5	0.76
Age (years)	57.4±16.0	47.9±13.9	0.18
NRS 2002 score	3.53±0.51	3.25±0.46	0.21
Lung cancer	5	1	
Breast cancer	4	4	
GI cancer	4	4	
Other cancer	2	0	

*p<0.05, indicating a significant difference.

Table 3. Improvements in the NRS2002 score and sarcopenia

	FSMP		Control		
	Before	After	Before	After	
NRS2002					X^2=4.19,
4	9	1	2	2	p=0.041**
3	8	1	6	2	
<3	0	15	0	4	
EWGSOP2					
Presarcopenia	0	0	1	1	
Sarcopenia	4	4	3	2	
AWGS2019					
Sarcopenia	3	3	3	1	
Severe sarcopenia	1	0	1	0	

*p<0.05, indicating a significant difference.

pre- and postintervention. Interleukin-6, interleukin-8, and tumour necrosis factor-alpha were not normally distributed and were excluded from the LMM. However, an increasing trend was observed for total muscle mass (p=0.062) and 25-OH vitamin D3 (p=0.053) levels, but these differences were not significant. For details, please refer to Table 4.

Correlation analysis

This study revealed that after adjusting for sex and age, the TUG score was negatively correlated with gait speed (PCC=-0.64, p=0.00) and 25-OH-VD3 (PCC=-0.341, p=0.01). Additionally, the TUG score was positively correlated with fat mass (PCC=0.439, p=0.00) and PLT (PCC=0.307, p=0.02). Conversely, gait speed was positively correlated with 25-OH-VD3 (PCC=0.359, p=0.01). Furthermore, gait speed was negatively correlated with IL-8 (PCC=-0.425, p=0.00) and PLT (PCC=-0.294, p=0.03). No significant correlations were found between gait speed and the various body composition measurements or serum biomarkers. Conversely, grip strength exhibited strong correlations with muscle mass (PCC=0.441, p=0.00), upper-limb muscle mass (PCC= 0.517, p=0.00), trunk muscle mass (PCC=0.544, p=0.00), Alb (PCC=0.374, p=0.00), and Hgb (PCC=0.322, p=0.02). Furthermore, grip strength was negatively correlated with the oedema index ECW (PCC=-0.418, p=0.00) and total triglycerides (PCC=-0.283, p=0.04).

DISCUSSION

Nutritional risk

This is the first randomized double-blind controlled trial aimed at comparing the effects of an FSMP intervention with those of an isocaloric control group on nutritional risk, sarcopenia, physical performance, muscle mass, inflammation markers, and serum biomarkers among cancer patients. The isocaloric control group mainly consisted of dextrin and soybean oil, while the FSMP contained relatively high levels of protein and various micronutrients and vitamins.

After follow-up, the NRS2002 score was significantly lower in the FSMP group than in the control group. This is predominantly because most patients were at nutritional risk owing to diminished food intake and weight loss resulting from cancer treatment over a previous span of time, leading to elevated NRS2002 scores. However, throughout the eight-week intervention, patients in the FSMP group secured superior scores regarding the stability of food intake and weight, which subsequently resulted in a decrease in their NRS2002 scores, extricating them from nutritional risk. Conversely, patients in the control group still suffered from food intake reduction and continuous weight loss. Although there was no significant difference in the rate of weight improvement between the two groups, this could be attributed to the limited sample size and the fact that patients at risk of malnutrition, particularly those afflicted with malignancies, necessitate an extended intervention period to achieve progressive weight gain.

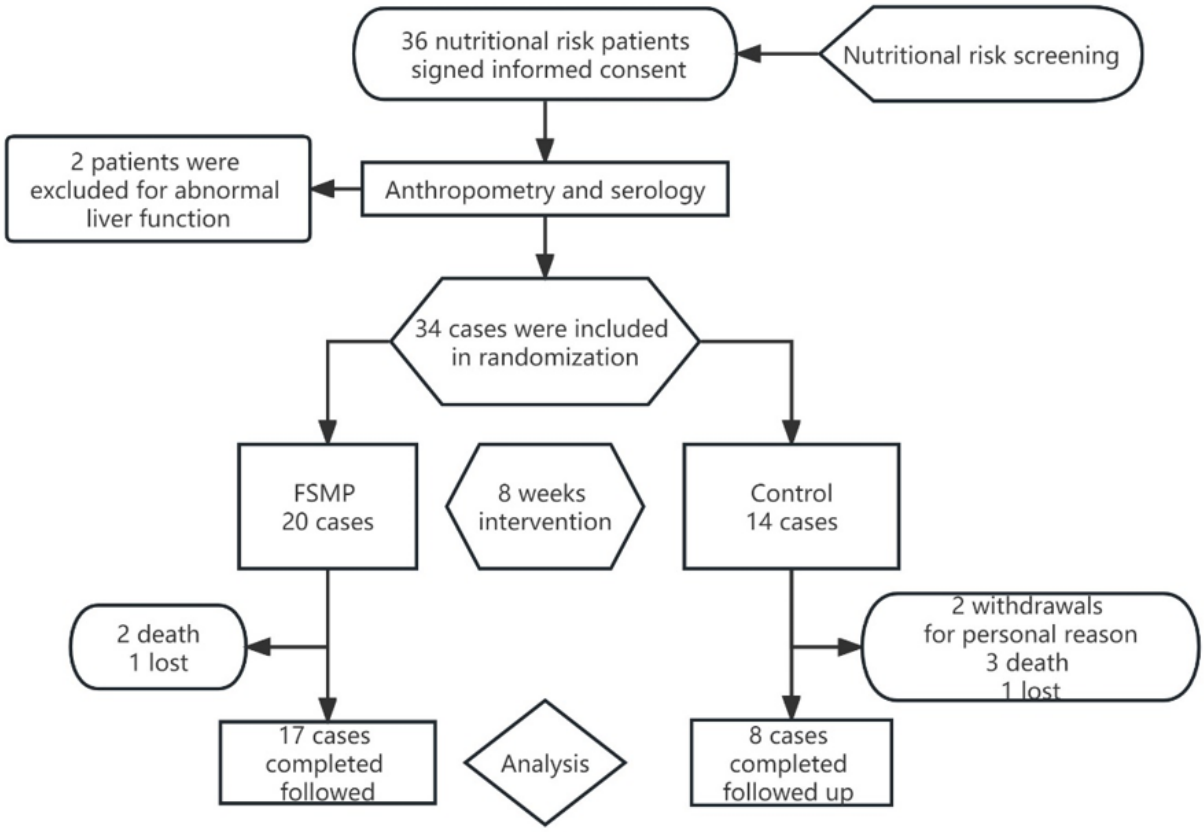

Figure 1. Study flowchart.

Table 4. Performance differences between the FSMP and control groups

Outcome Indicator	Mean (SD)				Difference (95% CI)	*p*
	Preintervention		Postintervention			
	FSMP Mean (SD)	Control Mean (SD)	FSMP Mean (SD)	Control Mean (SD)		
TUG (s)	8.46 (3.40)	7.36 (2.75)	6.59 (1.74)	9.06 (5.48)	-3.32 (-5.89, -0.74)	0.013*
Gait speed (m/s)	1.36 (0.63)	1.59 (0.49)	1.73 (0.39)	1.48 (0.50)	0.36 (0.06,0.66)	0.022*
Grip strength (kg)	26.2 (8.98)	21.5 (5.08)	28.4 (7.54)	21.1 (5.19)	3.56 (1.15,5.98)	0.006*
Calf (cm)	32.6 (4.36)	32.9 (2.73)	33.2 (2.95)	34.4 (2.13)	-1.13 (-2.93,0.67)	0.181
Total muscle mass (kg)	42.6 (9.37)	40.0 (5.27)	43.3 (8.48)	39.6 (5.70)	1.24 (-0.07, 2.55)	0.062
Upper-limb muscle mass (kg)	4.57 (1.47)	4.08 (0.94)	4.78 (1.40)	3.94 (0.94)	0.33 (0.02, 0.63)	0.037*
Trunk muscle mass (kg)	19.8 (4.21)	18.68 (3.01)	20.5 (4.05)	18.3 (3.03)	1.00 (0.26, 1.73)	0.010*
Lower-limb muscle mass (kg)	14.5 (3.33)	14.29 (3.32)	14.2 (3.07)	13.7 (2.97)	0.41 (-0.57, 1.40)	0.390
AMI (kg/m^2)	6.69 (1.13)	6.46 (0.94)	6.71 (1.04)	6.18 (0.65)	0.31 (-0.11, 0.74)	0.138
ASM (kg)	19.0 (4.71)	18.4 (4.07)	19.0 (4.40)	17.6 (3.71)	0.80 (-0.38, 1.97)	0.173
25(OH)VD3(ng/ml)	15.8 (11.29)	12.6 (5.48)	25.7 (17.6)	16.7 (7.62)	6.11 (-0.08, 1.29)	0.053
Alb (g/l)	41.2 (5.32)	43.6 (3.25)	42.1 (4.44)	42.9 (4.76)	0.40 (-2.94,3.74)	0.802
PA (mg/l)	218 (59.8)	271 (55.82)	247 (73.4)	264 (79.6)	-4.12 (-75.8,67.6)	0.905
Hs-CRP (mg/l)	9.46 (23.5)	1.91 (2.68)	2.39 (3.55)	14.5 (36.5)	-12.8 (-33.5,7.88)	0.214
T Lymphocytes (/ml)	915 (344)	1136 (914)	1019 (386)	976 (263)	125 (-105, 354)	0.268
Natural killer cells (/ml)	383 (260)	323 (392)	364 (253)	324 (394)	0.80 (-2.72,4.32)	0.635

Alb: serum albumin, AMI: appendicular skeletal muscle mass index, ASM: appendicular skeletal muscle mass, Calf: calf circumference,, PA: prealbumin. TUG: timed up-and-go test.
*$p<0.05$, indicating a significant difference.

Sarcopenia

Among the 34 randomly assigned patients in this study, 8 were diagnosed with sarcopenia according to the EWGSOP2 criteria, and 8 were diagnosed according to the AWGS2019 criteria, resulting in an overall prevalence of 23.5%. The patient populations largely overlapped. A recent narrative review revealed that the prevalence of sarcopenia ranged from 16% to 38.6% in patients with diverse cancers, including oesophageal and lung malignancies. The prevalence escalated with the duration of the cancer illness and the length of the treatment regimen, which included radiation and chemotherapy.[18]

However, due to the sample size of patients with sarcopenia who completed the intervention, no significant improvement in sarcopenia was observed. Nevertheless, the study revealed that the FSMP group primarily improved in terms of exercise capacity and upper-limb muscle mass, particularly in terms of improvements in the TUG test, gait speed, and grip strength. This suggests that simply providing caloric support may be insufficient for improving exercise performance and that a high-quality nutritional intervention is necessary. The EWGSOP recommends a daily caloric intake of 27-30 kcal/kg and a protein intake of 1.0-1.2 g/kg for older adults with limited mobility. In this study, nutritional intervention with FSMP increased protein intake by 0.18-0.25 g/kg/day and provided comprehensive supplementation of vitamins and micronutrients, achieving the goal of improving patients' exercise performance.[17] Similar findings have been supported by previous studies.[19-21] Sarcopenia is associated with quality of life in patients with advanced cancer.[22] Hence, adequate protein intake and appropriate intervention can improve sarcopenia in cancer patients, thereby enhancing their quality of life.

Moreover, the study revealed significant increases in upper-limb and trunk muscle mass in the FSMP group. However, no significant increases in lower-limb muscle mass were observed for the control group. Meanwhile, the total muscle mass did not significantly increase, so it is still not entirely clear in this study whether FSMP has a positive effect on muscle mass. This finding implies that factors influencing muscle mass are associated not only with nutritional and protein intake but also with physical activity. The patients in both groups exhibited varying degrees of daily activity and exercise, with a greater proportion engaging in walking, which might have led to the mixed outcomes in lower-extremity muscle mass.

Correlations

In this study, a correlation analysis was performed to determine the relationships among exercise performance, body composition, nutritional serum biomarkers, and inflammation markers in all patients. The findings indicated that diverse factors impacted the TUG score, gait speed, and grip strength. TUG and gait speed were significantly associated with IL-8, PLT, and 25-hydroxyvitamin D3. The TUG test, a prevalent clinical method used for screening exercise impairment and fall risk in older adults, has been found in previous research to be linked with gait speed, the Berg Balance Scale-BBS, and the Barthel Index.[23, 24] Age, cognitive status, muscle strength, and balance control also affect overall TUG test time in older adults.[25-27] Another study showed that elevated IL-6 and CRP levels are associated with an increased risk of MMD in older adults with slow gait speed.[28] IL-6 levels are associated with gait performance in community-residing seniors.[29] Increased levels of IL-8 and PLT indicate an inflammatory response in patients. This study revealed that the inflammatory levels in patients at nutritional risk may affect exercise capacity, suggesting the need to consider inflammation levels as a confounding factor in future studies on physical performance.

In contrast, grip strength exhibited a notable correlation with muscle mass, as measured by BIA. This finding concurs with previous studies that suggested an established correlation between grip strength and overall muscle mass.[30, 31] The aforementioned correlational findings further substantiate that gait speed, TUG performance and grip strength are assessments of sarcopenia conducted from distinct perspectives.

Intervention approach

Cancer patients often suffer from decreased appetite, nausea and vomiting due to chemotherapy, resulting in insufficient intake. The common enteral nutrition powders available in the Chinese market, such as Abbott's Ensure, only have two flavours—vanilla and wheat—that are very limited, and consumers have complained of sweetness, greasiness and monotony with these products, which in turn affects their intake. Therefore, local-flavour FSMPs became popular among patients early on due to their good taste and accessibility. This study is the first double-blind randomized controlled trial of local Chinese FSMP and clearly demonstrates the safety, acceptance, and significance of FSMP in improving physical performance. Some of the patients in this study took other enteral nutrition powders orally after the study, and they discovered after unblinding that the FSMP powder was more palatable, resulting in better compliance. The withdrawal of two patients in the control group was partially attributed to the taste of the powder, which they disliked. Hence, a more appealing taste contributes to achieving nutritional support goals and might result in improved nutrition, thereby improving quality of life.

Limitations

During the research period, due to the COVID-19 pandemic and societal efforts to control the outbreak, coupled with patients undergoing chemotherapy for malignant tumours, this study experienced a high mortality rate and loss to follow-up, thus presenting limitations in terms of sample size. In addition, due to the nonprescription nature of FSMP, participant adherence may be influenced by various factors, leading to frequent missed doses. Those who did not achieve the expected compliance rate during the intervention period were considered dropouts, resulting in some losses. In the future, we need to increase the sample size and stratify by cancer type to explore the heterogeneous effects of FSMP.

Although this study is one of the leading studies focusing on FSMP, revealing its interventional effects on cancer patients at nutritional risk and showing significant differences, The effects of FSMP may overlap with those of general nutritional support and not be unique to its

formulation. Future trials will compare FSMP with standard nutritional supplements to isolate its specific benefits. Therefore, to better illustrate the significance and effectiveness of this intervention, multicentre research with a larger sample size encompassing a wider range of patients is needed.

Conclusion

Through a double-blind randomized controlled intervention and long-term follow-up, this study revealed that comprehensive nutritional intervention with FSMP could improve nutritional risk, physical performance, and upper-limb muscle mass in cancer patients at nutritional risk compared to the isocaloric control group. However, there was no significant difference in the prevalence of sarcopenia or inflammatory indicators between pre- and post-intervention.

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CONFLICT OF INTEREST AND FUNDING DISCLOSURES

The authors declare no conflict of interest.

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Supplementary Table 1. Instruction for foods for special medical purposes

[Product category] Full nutritional formula food for special medical purposes.
[Ingredients] Maltodextrin, whey protein powder, camellia oil seed oil, low mustard acid rapeseed oil, soybean separation protein, crystalline fructose, oligofructose, inulin, sunflower seed oil, acetate vitamin A, vitamin D_3, dl-α-tocopherol acetate, plant menaquinone, thiamine hydrochloride, riboflavin, pyridoxine hydrochloride, cyanocobalamide, nicotinamide, folic acid, D-calcium pantothenate, L-ascorbate, D-biotin, sodium citrate, potassium chloride, copper sulfate, magnesium sulfate, ferrous sulfate, zinc sulfate, zinc sulfate, manganese sulfate, calcium carbonate, triccalcium phosphate, potassium iodate, sodium selenite, inositol, taurine, levocarnitine, phospholipid, vanillin.
[Formula characteristic / Nutrition characteristic] This product is full nutritional formula food for special medical purposes, in which the protein source is mainly why protein, and the protein energy supply ratio is 15%; fat energy supply ratio is 27%; carbohydrate energy supply ratio is 58%. Two dietary fibers, oligofructose and inulin, were added, adding 3.3g / 100g and 2.95g / 100g, respectively.
[Tissue status] Powder shape
[Eating method and consumption] Eating method: oral or tube feeding under the guidance of a doctor or clinical dietitian. Charging method: Add 1 bag (30g) of warm boiled water in about 110 mL (50~55℃), stir until dissolved, and prepare 130 mL standard punching solution. Consumption amount: should be under the guidance of doctors or clinical dietitian, according to the individual situation of the applicable population or medical conditions of the comprehensive deficiency.
[Net content and specification] 600 g (30 g 20bags)
[Shelf life] 24 months
[Storage conditions] Store at a cool and dry place at room temperature.
[Warning instructions and precautions]
1. Use it under the guidance of a doctor or a clinical dietitian.
2. Can be consumed alone as a single nutrient source.
3. This product is prohibited for parenteral nutrition support and intravenous nutrition.
4. Bacterial contamination should be avoided during use.
5. This product adds dietary fiber and should be used under the guidance of a doctor or a clinical dietitian.
6.Not applicable for use in the non-target population.
[Execution standard] Q / SLK 0203S
[Manufacturer] Zhejiang Haizheng Sulikkang Biotechnology Co., Ltd
[Company address] Room 301, No.293, East Workers' Road, Jiaojiang District, Taizhou City, Zhejiang Province
[Production address] No.46, Waisha Road, Jiaojiang District, Taizhou City, Zhejiang Province

Nutritional components	/100kJ	/100g	/100mL
Energy (kj)	100	1832	423
Protein (g)	0.9	16.2	3.7
Fat (g)	0.7	13.4	3.1
Linoleic acid (g)	0.10	1.80	0.40
α-Linolenic acid (mg)	21.8	399.9	92.3
Carbohydrate (g)	3.4	62.0	14.3
Vitamin A (μgre)	29	526	121
Vitamin D (μg)	0.6	10.3	2.4
Vitamin E (mg α -TE)	0.80	14.66	3.38
Vitamin K (μ g)	2.9	53.3	12.3
Vitamin B_1 (mg)	0.09	1.71	0.39
Vitamin B_2 (mg)	0.12	2.24	0.52
Vitamin B_6 (mg)	0.12	2.16	0.50
Vitamin B_{12} (μg)	0.21	3.85	0.89
Niacin (nicotinamide) (mg)	0.28	5.13	1.18
Folic acid (μg)	9	158	36
Pantothenic acid (mg)	0.44	8.08	1.86
Vitamin C (mg)	4.7	86.5	20.0
Biotin (μg)	2.1	39.0	9.0
Sodium (mg)	30	551	127
Potassium (mg)	40	736	170
Copper (μg)	26	476	110
Magnesium (mg)	6	118	27
Iron (mg)	0.4	6.4	1.5
Zinc (mg)	0.28	5.11	1.18
Manganese (μg)	68	1251	289
Calcium (mg)	28	504	116
Phosphorus (mg)	15	267	62
Iodine (μg)	5.0	91.8	21.2
Chlorine (mg)	29	531	123
Se (μg)	2.0	36.6	8.5
Bilineurine (mg)	5.6	102.6	23.7
Taurine (mg)	3.2	57.7	13.3
L-carnitine (mg)	4.7	85.7	19.8

Supplementary Table 2. Instruction for iso-caloric placebo

[Product category] Solid drinks
[Ingredients list] Maltodextrin, soybean oil, sunflower seed oil, phospholipid, sucralose, lemon yellow, vanillin
[Eating method] Add 1 bag (30g) with about 110 mL of warm boiling water (50~55℃), stir until it is dissolved and serve.
[Net content] 600 g (30g, 20bags)
[Shelf life] 24 months
[Storage conditions] Seal it and keep it in a cool, dry and dark place.
[Sensitizing substances] This product contains soy products.
[Product Standard Number] GB / T 29602
[Production License Number] SC10633100200168
[Production enterprise] Zhejiang Haizheng Sulikang Biotechnology Co., LTD
[Company address] Room 301, No.293 East Workers Road, Jiaojiang District, Taizhou City, Zhejiang Province
[Production address] No.46, Waisha Road, Jiaojiang District, Taizhou City, Zhejiang Province

	Every 100g	Nutrient reference value % or NRV %
Energy (kJ)	1878	22 %
Protein (g)	0	0 %
Fat (g)	14	23 %
Carbohydrate (g)	80	27 %
Sodium (mg)	100	5 %