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Supplementation Is Associated with Improved Body Composition and Clinical Recovery in Patients Undergoing Esophagectomy: A Prospective Controlled Pilot Study

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Research Article

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Abstract

Background

Esophageal cancer (EC) patients often suffer from postoperative malnutrition and sarcopenia due to a hypercatabolic state, which impairs recovery and prognosis. Whey protein isolate (WPI) is a promising oral nutritional supplement, yet its clinical effects in EC patients remain understudied. This study aimed to analyze the nutritional status of EC patients and investigate the efficacy of early postoperative whey protein supplementation on their body composition, nutritional-immune parameters and clinical outcomes.

Methods

A single-center, prospective non-randomized controlled pilot study was conducted at Fudan University Shanghai Cancer Center from November 2020 to October 2021, enrolling EC patients scheduled for radical resection. Patients were assigned to the control group (n = 139, November 2020–February 2021) receiving standard nutritional support and the whey protein (WP) group (n = 140, July–October 2021) with additional early oral whey protein supplementation (20 g/day) until discharge, on the basis of isonitrogenous and isocaloric nutritional plans. Body composition (fat mass, fat-free mass, skeletal muscle mass, etc.), serum nutritional and immune biomarkers (albumin, prealbumin, lymphocyte count, etc.), prognostic nutritional index (PNI) and postoperative length of stay (PLOS) were assessed at baseline (preoperatively) and before discharge. Statistical analysis was performed using SPSS 21.0, with $p < 0.05$ considered statistically significant.

Results

A total of 266 patients were included in the per-protocol analysis, with no significant differences in baseline demographic and clinical characteristics between the two groups. Whey protein supplementation was well-tolerated with no severe adverse events. Compared with baseline, the control group showed a decreasing trend in all body composition indicators except fat mass index (FMI) before discharge, while the WP group exhibited an increase in all body composition parameters, with significant intergroup differences. Both groups had decreased serum albumin, prealbumin, transferrin and retinol-binding protein (RBP) at discharge, but the reduction in lymphocyte count was significantly attenuated in the WP group ($p < 0.05$). PNI was below 46 in both groups at discharge with no significant intergroup difference, whereas the WP group had a significantly shorter PLOS than the control group. According to NRS 2002, only 6.8% of patients had high nutritional risk at baseline.

Conclusions

Early postoperative whey protein supplementation (20 g/day) on the basis of standard nutritional support effectively reverses postoperative weight loss, increases skeletal muscle mass and fat-free mass index, attenuates the reduction of peripheral lymphocytes, and shortens PLOS in EC patients. This intervention is safe and well-tolerated and can be integrated into the Enhanced Recovery After Surgery (ERAS) protocol for EC patients to optimize perioperative nutritional management. However, larger-scale multicenter randomized controlled trials with long-term follow-up are needed to confirm the sustained effects and determine the optimal supplementation dose for EC patients.

Trial registration

: This study was retrospectively registered with the Chinese Clinical Trial Registry on July 2, 2026 (Registration No.: ChiCTR2600127611).

Background

According to the latest GLOBOCAN 2022 estimates, esophageal cancer (EC) ranks as the 11th most prevalent malignancy globally and the 7th leading cause of cancer mortality, contributing to 2.6% of all new cancer diagnoses and 4.6% of cancer-related deaths[1, 2]. Approximately 4.8247 million new malignant tumor cases were diagnosed in China in 2022, with 2.5742 million deaths attributed to malignancies. Among these, 224,000 new esophageal cancer cases were reported, ranking 6th among all newly diagnosed malignancies. Esophageal cancer caused 187,500 deaths, making it the 5th leading cause of cancer-related mortality[3].Currently, the primary treatment for esophageal cancer remains surgery, supplemented by adjuvant therapies such as radiotherapy and chemotherapy. Surgical stress, coupled with impaired swallowing, anatomical alterations following gastrointestinal reconstruction, and anorexia, often induces a persistent hypercatabolic state in postoperative patients. Consequently, this leads to severe malnutrition and sarcopenia, which not only impedes functional recovery and quality of life but also increase susceptibility to infectious complications, potentially culminating in poor prognoses[4–8].

Nutritional support is indispensable for improving postoperative recovery and survival in patients undergoing esophageal cancer resection[9, 10]. Gustafsson et al. established the ERAS protocol, a multimodal pathway that incorporates routine postoperative nutritional support as a key component for patients undergoing upper gastrointestinal cancer surgery[11].

Whey protein isolate (WPI) represents a viable oral nutritional supplement (ONS) option for patients with cancer. Whey protein is abundant in cysteine and methionine, which act as key precursors for glutathione synthesis[12]. Consequently, it may mitigate the production of oxidative free radicals, reduce infection risk, and enhance immune function [13]. Moreover, under conditions of stress, whey protein (WP) can be efficiently absorbed and utilized by skeletal muscle, thereby promoting muscle protein synthesis[14, 15].

However, there remains a paucity of research, particularly clinical trials, investigating the beneficial effects of whey protein supplementation in patients with esophageal cancer. Therefore, the objective of this study was to analyze the nutritional status of esophageal cancer patients and to conduct a prospective non-randomized pilot study investigating the effects of postoperative whey protein supplementation in esophageal cancer patients.

Methods

Design and Subjects of This Study

A prospective, single center, non-randomized controlled pilot study of patients undergoing esophageal for patients with esophageal cancer was conducted, between November 2020 and October 2021, at the department of Thoracic Surgery at Fudan University Shanghai Cancer Center. Written informed consent was obtained from all participants prior to the study commencement. Inclusion criteria were as follows: (1) age ≥ 18 years; (2) pathological confirmation of esophageal cancer with planned radical resection; and (3) the ability to communicate effectively. Patients were allocated by admission date: the control group (November 2020-February 2021) and the WP group (July-October 2021). Exclusion criteria included: (1) concurrent malignancies; (2) a history of prior esophageal cancer surgery; (3) the presence of a cardiac pacemaker or arterial stent (which might interfere with body composition measurements); and (4) the development of life-threatening postoperative complications (e.g., major hemorrhage, severe infection) that would preclude study participation." The study was approved by the Hospital Ethics Committees (registration number: 2104233-22).

Nutritional Intervention

Both groups were prescribed individualized nutritional plans developed by the nutritional support team, targeting a daily energy intake of 25–30 kcal/kg and a protein intake of 1.2–1.5 g/kg. All patients underwent preoperative dietary counseling and initiated routine enteral nutrition within 2–3 days postoperatively.

Control Group: Patients received standard nutritional support as outlined above.

WP Group: In addition to the standard nutritional support, patients in this group received early oral supplementation with whey protein powder, supplied in individual sachets containing 25 g of powder (protein content: 80%), following the initiation of postoperative enteral nutrition. The supplementation regimen consisted of 10 g administered twice daily (bid) until the day prior to hospital discharge."

Measurements

Body weight and height were assessed with the same electronic scale. Prior to measurement, patients were asked to remove their outer clothing and shoes. Body composition such as fat mass (FM), fat-free

mass (FFM), protein and skeletal muscle (SM). Body mass index (BMI) was calculated using the formula: BMI = weight (kg) / height² (m²). Fat mass index (FMI) and fat-free mass index (FFMI) was calculated as FFM/height^2. Serum levels of albumin, prealbumin, transferrin, and retinol-binding protein (RBP), as well as lymphocyte count, were measured as biochemical and hematological indicators of nutritional status. The prognostic nutritional index (PNI) was calculated using the following formula: PNI = 10 × serum albumin (g/dL) + 0.005 × total lymphocyte count (per mm³)[16]. The Nutritional Risk Screening 2002 (NRS 2002) was used to evaluate nutritional status according to the guidelines of the European Society for Clinical Nutrition and Metabolism (ESPEN)[17].

The checkpoints for body composition analysis were conducted at baseline (preoperatively) and again before discharge. Demographic and clinical characteristics were collected at baseline prior to surgery. Laboratory parameters were assessed preoperatively and on postoperative days 1, 5, and 7, as well as prior to discharge.

Statistical Analysis

Statistical analysis was performed using SPSS software (version 21.0). Continuous variables with a normal distribution are presented as mean ± standard deviation ($\bar{x}$ ± SD) and were compared using the independent samples t-test. Continuous variables with a non-normal distribution are presented as median (inter-quartile range, IQR) and were compared using the Mann-Whitney U test. Categorical variables are presented as number (percentage) and were compared using the chi-square test or Fisher's exact test, as appropriate. All tests were two-tailed, and $p < 0.05$ was considered statistically significant.

Results

Baseline Characteristics

In total, 279 patients were recruited (Fig. 1) between November 2020 and October 2021. Patients were allocated by admission date: the control group (November 2020-February 2021, n = 139) and the WP group (July-October 2021, n = 140). Thirteen patients dropped out before the end of the study. All patients were included in the intention-to-treat (ITT) analysis, and 266 patients were included in the per-protocol (PP) efficacy analysis.

There were no significant differences in baseline characteristics or surgical variables between the two groups (Table 1). Treatment adherence remained high in both arms, and the administration of WP was well-tolerated, with no severe adverse events or mortalities reported.

Table 1
Characteristics of study sample

Characteristics	Control(n = 130)	Protein(n = 136)	*P* value
Gender n(%)			0.597
Male	112(86.2)	114(83.8)	
Female	18(13.8)	22(16.2)	
Age	64.04 ± 8.52	63.96 ± 7.85	0.940
Weight(kg)	62.23 ± 10.28	62.35 ± 10.20	0.921
BMI(kg/m^2)	22.07 ± 3.02	22.51 ± 2.78	0.217
Protein(kg)	9.97 ± 1.56	9.88 ± 1.49	0.618
FMI(kg/m^2)	4.93 ± 2.06	5.27 ± 1.91	0.154
FFMI(kg/m^2)	17.25 ± 1.89	17.35 ± 2.88	0.736
SM(kg)	32.43 ± 5.08	32.09 ± 4.85	0.573
Educational level n(%)			0.156
Primary school or below	52(40.0)	71(52.2)	
Junior high school	45(34.6)	37(27.2)	
Senior high school	23(17.7)	17(12.5)	
College or above	10(7.7)	11(8.1)	
Tumor location n(%)			0.067
Cervical esophageal cancer	1(0.8)	0(0)	
Thoracic esophageal cancer	127(97.7)	124(91.2)	
Abdominal esophageal cancer	2(1.5)	12(8.8)	
Albumin(g/l)	42.66 ± 3.74	42.87 ± 3.49	0.644
Transferrin(g/l)	2.14 ± 0.37	2.15 ± 0.31	0.843
Retinol-binding protein (RBP)(g/l)	32.76 ± 9.20	34.72 ± 9.15	0.077
NRS2002 Score			
1–2分	117	131	
3–5分	13	5	

According to the NRS 2002 score, only 18 patients (6.8%) were at a high risk of malnutrition (scores of 3, 4, and 5 were recorded in six patients each). All other patients had an NRS 2002 score<3 (93.2%).

Impacts of Whey protein on Body Composition and Clinical outcomes

The results of body composition and blood analysis comparing the baseline and before discharge impact of the nutritional intervention program are presented in Table 2 and Table 3. All values except FMI showed a decreasing trend in the control group before discharge. Conversely, all parameters in the WP group demonstrated an increase compared with baseline values. Statistically significant differences were detected between the two groups at baseline and before discharge.

Table 2 Body composition value evolution according to nutrition intervention program

		Control(n=130)	Protein(n=136)	*P*
Baseline	Weight(kg)	62.23±10.28	62.35±10.20	0.921
	BMI(kg/m^2)	22.07±3.02	22.51±2.78	0.217
	Protein(kg)	9.97±1.56	9.88±1.49	0.618
	SM (kg)	4.93±2.06	5.27±1.91	0.154
	FMI(kg/m^2)	17.25±1.89	17.35±2.88	0.736
	FFMI(kg/m^2)	32.43±5.08	32.09±4.85	0.573
Before discharge	Weight(kg)	62.12±10.01	63.87±9.36	0.142
	BMI(kg/m^2)	22.03±2.92	23.02±2.95	0.006
	Protein(kg)	9.92±1.55	9.99±1.35	0.683
	SM (kg)	32.22±5.07	32.48±4.66	0.666
	FMI(kg/m^2)	4.97±1.94	5.54±1.99	0.019
	FFMI(kg/m^2)	17.16±1.94	17.57±2.76	0.167
Increase	Weight(kg)	-1.07±4.04	1.52±4.04	0.000
	BMI(kg/m^2)	-0.45±1.05	0.51±0.94	0.000
	Protein(kg)	-0.52±0.56	0.11±0.60	0.020
	SM (kg)	-0.21±1.82	0.39±2.02	0.012
	FMI(kg/m^2)	0.05±0.87	0.27±0.68	0.021
	FFMI(kg/m^2)	-0.92±0.95	0.21±1.01	0.012

With the exception of RBP, the values of both groups decreased before discharge Nutritional intervention, involving the supplementation of whey protein, failed to prevent the decrease in serum albumin, prealbumin, transferrin and RBPlevels. The reduction in lymphocyte count was significantly attenuated in the WP group relative to the CONTROL group ($p < 0.05$) (Table 3).

Table 3 Changes in nutrition-related blood markers according to nutrition intervention program

		Control(n=130)	Protein(n=136)	*P*
Baseline	Albumin(g/l)	42.66±3.74	42.87±3.49	0.644
	Prealbumin(g/l)	236.77±56.84	244.99±53.49	0.225
	Transferrin(g/l)	2.14±0.37	2.15±0.31	0.843
	Retinol-binding protein(g/l)	32.76±9.20	34.72±9.15	0.077
	Lymphocyte count(*10^9/l)	1.59±0.50	1.68±0.50	0.147
Before discharge	Albumin(g/l)	37.84±3.35	37.40±3.10	0.331
	Prealbumin(g/l)	198.80±56.96	206.39±58.81	0.253
	Transferrin(g/l)	1.94±0.43	2.07±2.23	0.317
	Retinol-binding protein(g/l)	34.32±11.23	33.00±10.53	0.372
	Lymphocyte count(*10^9/l)	1.32±0.45	1.23±0.44	0.053
Decrease	Albumin(g/l)	4.81±4.72	5.47±3.40	0.458
	Prealbumin(g/l)	37.97±53.01	38.60±70.53	0.683
	Transferrin(g/l)	0.20±0.34	0.07±2.15	0.588
	Retinol-binding protein(g/l)	-1.57±10.22	1.75±35.45	0.073
	Lymphocyte count(*10^9/l)	0.27±0.486	0.45±0.356	0.001

*Decrease = (Baseline) – (Pre-discharge).

At discharge, the PNI was below 46 in both groups, with no statistically significant intergroup difference observed. In contrast, the WP group exhibited a significantly shorter PLOS compared with the CONTROL group (Table 4).

Table 4 Comparison of PNI and postoperative length of stay

Characteristics	Control(n=130)	Protein(n=136)	*P*
PNI	44.46±4.71	43.56±3.66	0.080
PLOS(d)	15.85±13.07	11.79±8.84	0.003

*PLOS: postoperative length of stay

Discussion

Esophageal cancer (EC) remains a major global health burden, with surgery as the cornerstone of curative treatment. However, postoperative hypercatabolic states induced by surgical stress, swallowing dysfunction, and anatomical reconstruction often lead to malnutrition, sarcopenia, and increased

infectious complications, which severely affect patient recovery and prognosis[3, 5]. Nutritional support, as a key component of the Enhanced Recovery After Surgery (ERAS) protocol, has been proven essential for improving perioperative outcomes of EC patients[11]. Whey protein, with its high bioavailability, rich essential amino acids, and immunomodulatory properties, has emerged as a promising oral nutritional supplement (ONS) for cancer patients[12, 13]. This prospective non-randomized pilot study systematically evaluated the effects of early postoperative whey protein supplementation on body composition, nutritional-immune parameters, and clinical recovery in EC patients, providing valuable evidence for optimizing perioperative nutritional management in EC.

Key Findings and Clinical Implications

1. Reversal of Postoperative Muscle Wasting: Core Value of Whey Protein Supplementation

Skeletal muscle mass loss and sarcopenia are prominent issues in EC patients after surgery, directly related to poor functional recovery and increased complication rates[7]. The present study found that, on the basis of isonitrogenous and isocaloric standard nutritional support, adjuvant whey protein supplementation (20 g per day) effectively abrogated the postoperative tendency toward weight loss, significantly elevated skeletal muscle mass (SM) and fat-free mass index (FFMI). This is consistent with the biological characteristics of whey protein: its rich branched-chain amino acids (especially leucine) can efficiently activate the mammalian target of rapamycin (mTOR) signaling pathway, thereby promoting skeletal muscle protein synthesis[18, 19]. Unlike other proteins, whey protein is rapidly absorbed and utilized, which is particularly critical for counteracting the hypercatabolic state in the early postoperative period[13]. A meta-analysis of perioperative protein supplementation in cancer patients also confirmed that whey protein can improve muscle function and reduce muscle loss[15], which is further supported by our findings.

Notably, the control group showed a decreasing trend in all body composition indicators except fat mass index (FMI) before discharge, while the whey protein (WP) group showed an increase in all parameters. This suggests that conventional nutritional support alone may be insufficient to offset the postoperative catabolic stress, and targeted whey protein supplementation can effectively tip the balance toward anabolism. For EC patients, maintaining muscle mass is not only important for short-term postoperative recovery but also for long-term functional maintenance and quality of life[6], highlighting the clinical significance of this intervention.

2. Differential Responses of Nutritional and Immune Markers: Insights into Intervention Efficacy

A notable finding of this study is the differential response of various nutritional and immune markers to whey protein supplementation. While serum albumin, prealbumin, transferrin, and retinol-binding protein (RBP) decreased in both groups before discharge, the reduction in lymphocyte count was significantly attenuated in the WP group ($p < 0.05$). Additionally, the WP group showed a significant increase in serum total protein levels. This discrepancy can be explained by multiple mechanisms:

First, serum albumin and prealbumin are not only nutritional markers but also acute-phase reactants. Postoperative surgical stress and inflammatory responses can lead to decreased synthesis and increased consumption of these proteins, which may override the beneficial effects of nutritional supplementation in the short term[20–22]. Similar results were observed in a study of endometrial cancer patients, where 20 g/day of protein supplementation failed to maintain serum albumin and prealbumin levels, possibly due to the overwhelming impact of surgical inflammation[20]. Second, lymphocytes, as key immune cells, are more directly regulated by whey protein. Whey protein is rich in cysteine and methionine, which are precursors for glutathione synthesis, and can enhance immune function by reducing oxidative stress and inhibiting inflammatory cytokine production[12, 20]. Moreover, α-lactalbumin, a major component of whey protein, can inhibit the production of pro-inflammatory cytokines in monocytes, thereby protecting immune cells[23].

The prognostic nutritional index (PNI), calculated based on albumin and lymphocyte count, was below 46 in both groups at discharge with no significant intergroup difference. This indicates that although whey protein supplementation alleviated lymphocyte reduction, the persistent decrease in albumin limited the improvement of PNI. Given that PNI is a well-validated prognostic marker for cancer patients[16], long-term follow-up is needed to determine whether prolonged whey protein supplementation can improve PNI and long-term outcomes. Additionally, combining nutritional supplementation with exercise may further enhance the effect, as resistance training can induce the release of anabolic hormones and growth factors, synergistically promoting protein synthesis and immune function[19, 24].

3. Improvement of Clinical Recovery: Reduction in Postoperative Hospital Length of Stay

The WP group exhibited a significantly shorter postoperative length of stay (PLOS) compared with the control group, which is a key clinical outcome of the ERAS protocol. This finding aligns with a meta-analysis showing that whey protein supplementation improves perioperative functional capacity and reduces postoperative complications in cancer patients[15]. The potential mechanisms include: Improved muscle function and nutritional status enhancing the patient's ability to tolerate early ambulation and rehabilitation training; Attenuated immune suppression reducing the risk of infectious complications, which are major causes of prolonged hospital stay[5, 25]; Rapid nutrient absorption and utilization promoting wound healing and gastrointestinal function recovery[13, 21].

In a study of 33 EC patients, perioperative whey protein supplementation reduced the incidence of postoperative infectious complications (24% vs. 49%, $p < 0.05$)[26], which may indirectly contribute to shortened PLOS. Although the present study did not focus on complication rates, the reduction in PLOS strongly suggests improved overall recovery, which is consistent with the core goals of ERAS.

4. Mechanistic Insights into the Beneficial Effects of Whey Protein

The multifaceted benefits of whey protein observed in this study are supported by extensive mechanistic research. Beyond promoting muscle protein synthesis via the mTOR pathway[18, 19], whey protein exerts

anti-inflammatory effects by inhibiting cyclooxygenase-2 (COX-2) and phospholipase A_2 (PLA_2)[23], thereby reducing the production of pro-inflammatory mediators such as interleukin-6 (IL-6) and prostaglandin E_2 (PGE_2). In sarcopenic older adults, supplementation with vitamin D and leucine-enriched whey protein was shown to attenuate chronic low-grade inflammation[18], which may also be relevant for EC patients with postoperative inflammatory responses.

Furthermore, whey protein's high bioavailability ensures rapid delivery of amino acids to tissues, which is crucial for overcoming postoperative anabolic resistance[19]. Unlike plant-based proteins or casein, whey protein stimulates muscle protein synthesis more effectively, especially in the context of stress and inflammation[23, 24]. These mechanisms collectively contribute to the improvements in body composition, immune function, and clinical recovery observed in the WP group.

Comparison with Previous Studies

The findings of this study are generally consistent with previous research on whey protein supplementation in cancer patients. A systematic review and meta-analysis of 10 RCTs found that whey protein supplementation significantly reduced postoperative complications (OR = 0.61, 95% CI 0.41–0.90) and improved functional capacity (6-minute walk test) in cancer patients[15], which aligns with our observations of reduced PLOS and improved body composition. Similarly, a study of EC patients showed that perioperative whey protein supplementation reduced infectious complications [8], further supporting the efficacy of this intervention.

However, there are some differences between this study and previous work. For example, a study of endometrial cancer patients found that 20 g/day of protein supplementation did not maintain serum nutritional markers[20], which is consistent with our finding that albumin and prealbumin continued to decrease. This suggests that the dose of 20 g/day may be insufficient to counteract the severe inflammatory response and catabolism induced by major surgery, and higher doses (e.g., 30–40 g/day) or longer intervention durations may be needed[15, 20]. Additionally, some studies have reported improvements in albumin and prealbumin with whey protein supplementation[10, 14], which may be due to differences in patient populations (e.g., nutritional status at baseline, type of surgery) and intervention timing (preoperative vs. postoperative supplementation).

Another point of note is that this study did not find a significant difference in PNI between groups, while other studies have reported improvements in PNI with nutritional supplementation[16]. This discrepancy may be attributed to the short intervention duration (until discharge) and the overwhelming impact of postoperative inflammation on albumin levels. Future studies with longer follow-up (e.g., 1–3 months postoperatively) may better reflect the effect of whey protein on PNI.

Strengths and Limitations

Strengths

This study has several notable strengths. First, it is one of the few prospective studies to systematically assess the effects of early postoperative whey protein supplementation on body composition (using precise bioelectrical impedance analysis), nutritional-immune parameters, and clinical outcomes in EC patients. Second, the study design strictly controlled for energy and protein intake between groups, ensuring that the observed effects were attributable to whey protein rather than differences in total nutrient intake. Third, the intervention was well-tolerated with no severe adverse events, demonstrating its safety and feasibility in clinical practice. Fourth, the study provides detailed data on multiple markers, offering insights into the mechanisms of whey protein's effects.

Limitations

Despite these strengths, this study also has some limitations. First, it is a single-center, non-randomized pilot study with a relatively small sample size (266 patients in the per-protocol analysis), which may limit the generalizability of the results. Randomized controlled trials with larger sample sizes are needed to confirm the findings. Second, the intervention duration was limited to the postoperative period until discharge, and long-term follow-up data (e.g., 3–6 months postoperatively) are lacking to evaluate the sustained effects on muscle function, nutritional status, and long-term prognosis. Third, the study did not assess the impact of whey protein supplementation on postoperative complications (e.g., pulmonary infection, anastomotic leakage), which are important outcomes for EC patients. Future studies should include complication rates as a primary outcome. Fourth, the study did not stratify patients by baseline nutritional status (e.g., NRS 2002 score ≥ 3 vs. <3), and it is unclear whether patients with high nutritional risk derive greater benefits from the intervention. Fifth, the dose of whey protein (20 g/day) was fixed, and the optimal dose for EC patients remains to be determined.

Future Research Directions and Clinical Implications

Based on the findings and limitations of this study, several future research directions and clinical implications can be proposed. In terms of clinical practice, early postoperative whey protein supplementation (20 g/day) should be considered as part of the ERAS protocol for EC patients, especially those at risk of muscle loss and immune suppression. To maximize efficacy, supplementation may need to be combined with preoperative nutrition (prehabilitation) and postoperative exercise training[19, 22], as multimodal interventions have been shown to be more effective than single interventions[4, 15, 27]. Additionally, monitoring of lymphocyte count and body composition (rather than just albumin) may better reflect the efficacy of nutritional interventions in the early postoperative period.

In terms of future research, first, large-scale, multicenter randomized controlled trials are needed to confirm the effects of whey protein supplementation on PLOS, complication rates, and long-term prognosis in EC patients. Second, dose-response studies should be conducted to determine the optimal dose of whey protein for EC patients (e.g., 20 g/day vs. 30 g/day vs. 40 g/day). Third, studies stratifying patients by baseline nutritional status and sarcopenia status are needed to identify subgroups that derive the greatest benefit from the intervention. Fourth, long-term follow-up studies should evaluate the

sustained effects of whey protein on muscle function, quality of life, and survival. Fifth, mechanistic studies should further explore the molecular pathways through which whey protein improves immune function and reduces inflammation in EC patients.

Conclusions

In conclusion, this prospective pilot study demonstrates that early postoperative whey protein supplementation (20 g/day) on the basis of standard nutritional support effectively reverses postoperative weight loss, increases skeletal muscle mass and fat-free mass index, attenuates lymphocyte reduction, and shortens postoperative hospital length of stay in EC patients. These findings support the integration of whey protein supplementation into the ERAS protocol for EC patients, providing a safe and effective strategy to improve perioperative recovery. However, larger-scale, long-term studies are needed to confirm these results and optimize the intervention regimen.

Abbreviations

Abbreviation
Full name
EC
Esophageal Cancer
WPI
Whey Protein Isolate
WP
Whey Protein
ERAS
Enhanced Recovery After Surgery
ONS
Oral Nutritional Supplement
BMI
Body Mass Index
FM
Fat Mass
FFM
Fat-Free Mass
FMI
Fat Mass Index
FFMI
Fat-Free Mass Index
SM
Skeletal Muscle
RBP

Retinol-Binding Protein
PNI
Prognostic Nutritional Index
NRS 2002
Nutritional Risk Screening 2002
PLOS
Postoperative Length of Stay
ITT
Intention-to-Treat
PP
Per-Protocol
mTOR
Mammalian Target of Rapamycin
COX-2
Cyclooxygenase-2
PLA_2
Phospholipase A_2
IL-6
Interleukin-6
PGE_2
Prostaglandin E_2
RCT
Randomized Controlled Trial
ESPEN
European Society for Clinical Nutrition and Metabolism
GLOBOCAN
Global Cancer Observatory

Declarations

Ethics approval and consent to participate

This study was approved by the Fudan University Shanghai Cancer Center Ethics Committee(Approval Number: 2104233-22). Written informed consent was obtained from all participants prior to the commencement of the study, including consent for participation in the study and the use of clinical data for research purposes. We confirm that our study was conducted in full compliance with the principles of the Declaration of Helsinki (https://www.wma.net/policies-post/wma-declaration-of-helsinki/).

Consent for publication

All participants provided written informed consent prior to study enrollment, which included consent for the publication of anonymized data and study results. This manuscript does not contain any individual person's identifiable data (including personal details, images, or videos) that could lead to the identification of participants. The institutional ethics committee (Fudan University Shanghai Cancer Center, approval number: 2104233-22) has approved the publication of the study's anonymized findings.

Competing interests

The authors declare that they have no competing interests.

Authors' information

Not applicable.

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Author Contribution

Yiqun Ling conceptualized and designed the study; Chong Chen, Qiong Wang and Tianhao Ni collected and curated the clinical data; Hua Zhang and Huiping Ding performed the statistical analysis; Liuqing Xu drafted the original manuscript; all authors revised the manuscript critically for important intellectual content, read and approved the final version of the manuscript, and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Liuqing Xu, Hua Zhang, Chen Chong and Tianhao Ni contributed equally to this work and are co-first authors.

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Availability of data and materials

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request, in compliance with the ethical guidelines for human subject research and privacy protection regulations. No additional public datasets were used or analyzed in this study.

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Figures

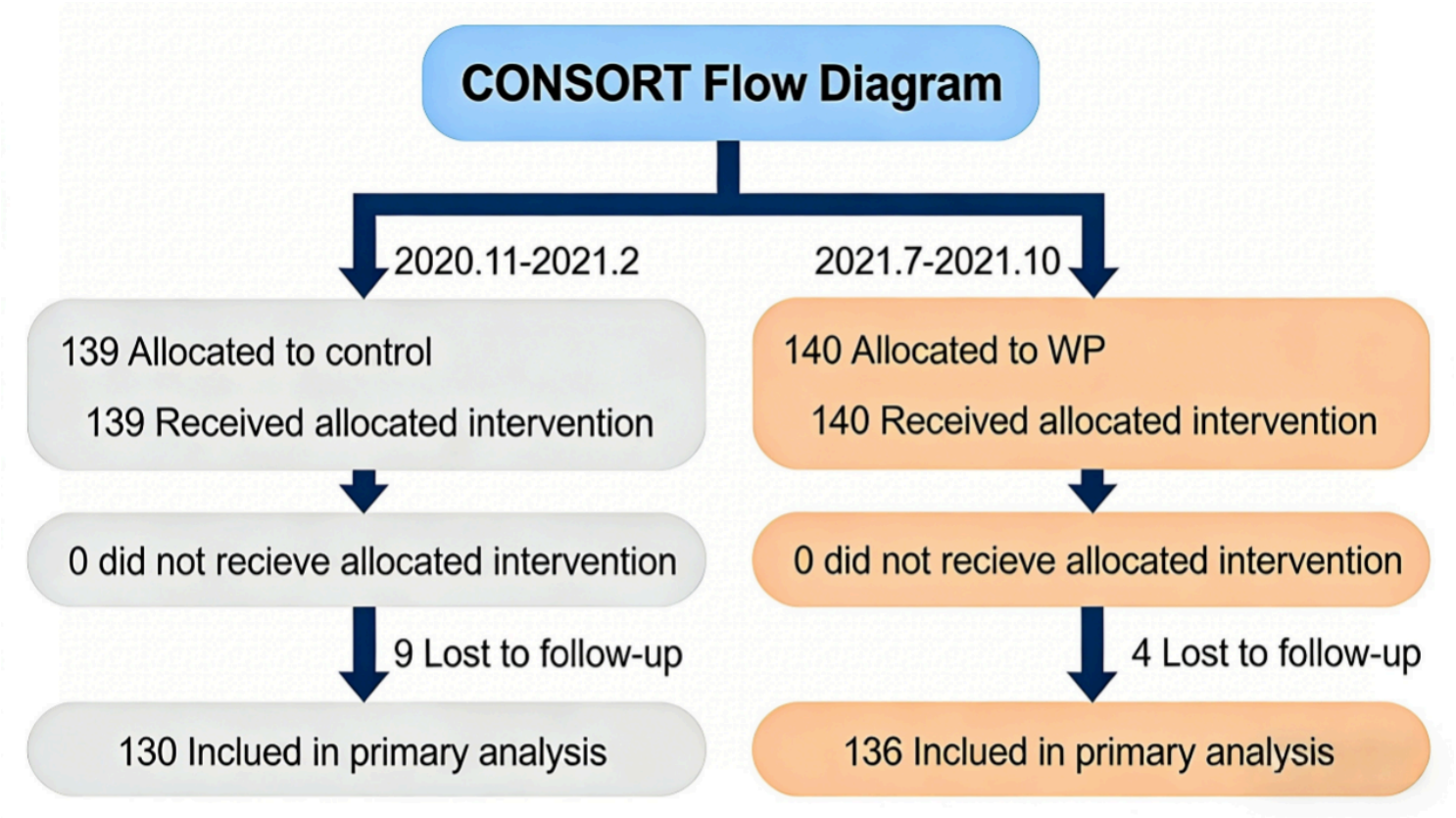


Figure 1

Flow chart of the study. WP: whey protein