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Cellular-Level Nutritional Repletion and Survival Outcomes in Stage IV Metastatic Cancer: A 48-Month Follow-Up Study

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ABSTRACT

Background: Cancer remains one of the most prevalent and life-threatening diseases of the modern era, driven by complex genetic and epigenetic factors. The pathogenesis of chronic malignancy is primarily dominated by three critical mechanisms: systemic inflammation, oxidative stress, and endothelial dysfunction. Maintaining the integrity of these cellular processes is vital for health preservation. In this context, micronutrients such as vitamins, trace elements, and minerals play a fundamental role. However, cancer patients often suffer from severe malnutrition, cachexia, and significant weight loss due to the disease progression or the side effects of chemotherapy and radiotherapy, such as nausea and loss of appetite. This nutritional decline severely impairs the quality of life and is a major contributor to early mortality.

Aim: This study aimed to evaluate the efficacy of a targeted nutritional intervention using ***five specific functional food supplements*** to reverse malnutrition-related appetite loss and weight reduction. The investigation focused on whether achieving cellular saturation with key ***micronutrients, macronutrients, and pro-prebiotics*** could modulate inflammatory and oxidative pathways, thereby improving nutritional status and survival outcomes in Stage IV metastatic cancer patients.

Methods: The study cohort consisted of 98 adult patients (51 men, 47 women; median age 61) with Stage IV metastatic stomach (n=18), breast (n=18), colon (n=18), lung (n=24), and pancreatic cancer (n=20) who had completed conventional treatments. Initial body weights were critically low, ranging between 31–44 kg. The 48-month intervention involved a daily oral regimen of: *Morinda citrifolia* (anti-atherosclerotic liquid- AAL), *Omega-3*(anti-inflammatory capsules- AIC), *Alaskan blueberry and 21 red-purple fruit-vegetable extract* (antioxidant liquid- AOL), *collagen* (type1-3 collagen liquid-CL) and *pro-prebiotic* (Pro-prebiotic capsules- PPC). In the first 12 months, only 3 food items were given, but in the following 3 years, patients were given two more food items containing collagen and pro-prebiotics.

Results: At the end of the first year, 74 of the 98 patients survived. By the fourth year, 42 patients remained alive, with their body weights significantly increasing to a range of 55–81 kg. The synergistic effect of antioxidant liquid (AOL), anti-inflammatory capsules (AIC), anti-atherosclerotic liquid (AAL), collagen liquid (CL), and pro-prebiotic capsules (PPC) ensured the restoration of essential nutrient levels at the cellular level. This intervention effectively prevented malnutrition, leading to a substantial increase in appetite and sustainable weight gain.

Conclusion: Targeted micronutrition, incorporating vitamins, minerals, collagen, and pro-prebiotics, addresses the root causes of malnutrition in advanced cancer. By correcting cellular deficiencies, this approach significantly improves appetite, promotes weight gain, and enhances both the quality of life and long-term survival in metastatic patients.

Introduction

Cancer continues to be a major global contributor to morbidity and mortality: roughly one in five individuals is diagnosed before age 75, and close to half of these diagnoses are ultimately fata[1]. Although early detection and therapeutic options have improved markedly, cancer management remains challenging because its origins are multifactorial, encompassing both genetic and epigenetic influences[2,3].

Growing evidence suggests that lifestyle factors, particularly nutrition, may influence not only cancer prevention but also the course of established malignancy, including possible regression. Both the cancer process and anticancer therapies such as chemotherapy and radiotherapy frequently contribute to weight loss, muscle depletion, and worsening nutritional status[4,5]. Nutritional impairment is linked to low BMI and sarcopenia, which can reduce treatment tolerance, heighten toxicity, and ultimately worsen clinical outcomes[6-9]. Beyond these clinical consequences, malnutrition may amplify key cancer-related pathophysiologic pathways—namely chronic inflammation, oxidative stress, and endothelial dysfunction—processes that are each implicated in tumor progression[10-15]. Cellular nutrition has been shown to play a key role in achieving and maintaining good health, not only in cancer and similar chronic diseases, but also in perfectly healthy individuals[15,16].

Vitamins, minerals, and trace elements—key micronutrients—are required to preserve cellular integrity and to modulate these fundamental biological pathways[3]. Also in cancer cachexia, accumulating evidence links gut dysbiosis to inflammatory and metabolic derangements, and microbiota-modulating strategies (including **probiotics, prebiotics, and synbiotics**) have shown encouraging-though still preliminary-signals in cachexia-related outcomes[17]. The gut microbiota–intestine axis has been proposed as an unexpected but plausible therapeutic target in cachexia, warranting more patient-level mechanistic and interventional studies[18]. Accumulating data indicate that targeted nutrition strategies can support the restoration of cellular homeostasis by dampening inflammation, lowering oxidative stress, and enhancing endothelial function[5]. This is particularly important in cancer, where malnutrition reflects not only calorie shortfall but also complex metabolic and molecular alterations. Poor nutritional status in cancer is frequently manifested by **low muscle mass**, which is clinically relevant across disease stages; therefore, nutrition interventions-including adequate **protein and oral nutritional supplement (ONS)** strategies—represent an important opportunity to prevent or mitigate muscle depletion[19].

However, long-term evidence on integrated, micronutrient-focused supplementation strategies that target these pathways in stage IV metastatic cancer remains limited. Moreover, progressive weight loss and nutritional decline in advanced cancer are closely linked to reduced survival and impaired quality of life, underscoring the clinical importance of early recognition and sustained nutritional support[12]. In this study, we investigate a novel strategy to address malnutrition-associated anorexia and weight loss through the administration of five functional food supplements intended to optimize these cellular pathways.

By assessing how these supplements influence inflammatory biomarkers, oxidative stress measures, and endothelial function, we aim to test whether increasing cellular micronutrient sufficiency can translate into improved nutritional status, greater appetite, weight gain, and, ultimately, better quality of life and survival among patients with cancer[13,15].

Material and Methods

STUDY DESIGN AND PARTICIPANTS

This quasi-experimental pre–posttest study[20] was conducted at the Epigenetic Health Center Outpatient Clinics in Ankara, Türkiye, from December 1, 2018, to June 1, 2021. The study design adhered to the TREND[21] statement checklist for nonrandomized evaluations of behavioral and public health interventions. No additional patients were enrolled after 2021. Follow-up continued for up to 48 months, with the last follow-up visit completed on 1 November 2025.

Participants were selected based on the following inclusion criteria: individuals older than 18 years with systolic blood pressure ≤140 mmHg and/or diastolic blood pressure ≤90 mmHg, and a normal estimated glomerular filtration rate (eGFR ≥90 mL/min).

Patients were excluded if they had a history of treatment with angiotensin converting enzyme

inhibitors or angiotensin receptor blockers, obesity (BMI >30 kg/m²), dyslipidemia (total cholesterol >280 mg/dL and/or fasting triglycerides >180 mg/dL), renal failure (eGFR <90 mL/min), nephrotic syndrome (urinary protein excretion >3000 mg/day), or a history of cardiovascular disease (evidenced by abnormal electrocardiogram, smoking, or recent/current use of statins).

Out of 261 patients who met the inclusion criteria, 98 patients (predominantly male, 51 M, with a mean age of 58 ± 14 years) with chronic diseases were enrolled in the study. These 98 patients; diagnosed with Stage 4 metastatic cancers—including stomach (n=18), breast (n=18), colon (n=18), lung (n=24), and pancreatic cancer (n=20)—who had completed chemotherapy and radiotherapy treatments. The study was conducted over *a 48-month period and comprised* 51 men and 47 women, with a median age of 61 years (range 26–87 years) and an initial body weight between 31 and 44 kg.

BASELINE EVALUATION

At baseline, each patient underwent a comprehensive evaluation that included a standard physical examination, chest X-ray, baseline electrocardiogram, and two-dimensional echocardiography. Routine clinical laboratory tests were performed, which included assessments of liver and kidney function and 24-hour urinary protein measurements. Arterial blood pressure was recorded in the right arm using a mercury sphygmomanometer in a resting condition (three separate measurements in the morning with the mean value calculated).

MEASUREMENTS

Blood chemistry: Morning blood samples were collected from patients after 12 hours of fasting. Subjects were asked to refrain from physical activity for at least 30 minutes prior to the blood draw. In addition to routine clinical laboratory tests, serum asymmetric dimethylarginine (ADMA), malondialdehyde (MDA), copper zinc-superoxide dismutase (CuZn-SOD), glutathione peroxidase (GSH-Px), high sensitivity C reactive protein (hsCRP) and pentraxin 3 (PTX3) concentrations and basal insulin levels were analyzed from all patients. After the intervention period, blood samples were obtained for the measurement of serum ADMA, MDA, CuZn-SOD, GSH-Px, hsCRP and PTX3 concentration. The measurement of total cholesterol (TC), triglyceride (TG), high-density lipoprotein (HDL) cholesterol and fasting plasma glucose (FPG) was performed by enzymatic colorimetric method with Olympus AU 600 auto analyzer using reagents from Olympus Diagnostics, GmbH (Hamburg, Germany). Low-density lipoprotein (LDL) cholesterol was calculated by Friedewald's formula[22].

Serum basal insulin values were determined by the coated tube method (DPC-USA). In particular, insulin resistances index Homeostasis Model Assessment-Insulin resistance (HOMA-IR) was computed with the formula: (HOMA-IR) = FPG (mg/dl) x immunoreactive insulin (IRI) (μIU/ml)/ 405[23]. All samples were run in triplicates.

Asymmetric dimethylarginine (ADMA) measurements: Measurements of serum ADMA were done using high performance liquid chromatography (HPLC), as described by Chen et al. [24]. In brief, 20 mg of 5-sulfosalisilic acid (5-SSA) was added to 1 ml serum and the mixture was left in an ice-bath for 10 min. The precipitated protein was removed by centrifugation at 2000 g for 10 min. Ten micro liters of the supernatant which was filtered through a 0.2 μm filter was mixed with 100 μl of derivatization reagent (prepared by dissolving 10 mg o-phtaldialdehyde in 0.5 ml of methanol, 2 ml of 0.4 M borate buffer (pH 10.0) and 30 μl of 2-mercaptoethanol) and then injected into the chromatographic system. Separation of ADMA was achieved with a 150x4 mm I.D. Nova-pak C18 column with a particle size of 5 μm (Waters, Millipore, Milford, MA, USA) using 50 mM sodium acetate (pH 6.8), methanol and tetrahydrofurane as mobile phase (A, 82:17:1; B, 22:77:1) at a flowrate of 1.0 ml/min. The area of peak detected by the fluorescent detector (Ex: 338 nm) was used as quantification. The variability of the method was less than 7%, and the detection limit of the assay was 0.01 μM.

High sensitive C reactive protein (hsCRP) assessment: Briefly, serum samples were diluted with a ratio of 1/101 with the diluent's solution. Calibrators, kit controls and serum samples were all added on each micro well with an incubation period of 30 minutes. After 3 washing intervals 100 μL enzyme conjugate (peroxidase labeled anti-CRP) was added on each micro well for additional 15 minutes incubation in room temperature in dark. The

reaction was stopped with a stop solution and photometric measurement was performed at the 450 nm wavelength.

Plasma Pentraxin (PTX-3) measurements: Plasma PTX 3 concentration was measured posteriori from frozen samples by using a commercially available enzyme-linked immunosorbent assay (ELISA) kit (Perseus Proteomics Inc, Japan).

Erythrocyte antioxidant capacity: Blood samples were drawn after overnight fasting from the antecubital vein and collected in heparinized polypropylene tubes. Plasma and erythrocytes were separated and used for measuring trace elements and antioxidant enzymes. Erythrocyte CuZn-SOD and GSH-Px activity was measured in a UV-VIS Recording Spectrophotometer (UV-2100S; Shimadzu Co., Kyoto, Japan) as previously described by Aydin et al. [25]. Erythrocyte zinc (Zn), copper (Cu), and iron (Fe) levels were measured by flame atomic absorption spectrophotometry using a Varian atomic absorption spectrophotometer (30/40 model; Varian Techtron Pty Ltd., Victoria, Australia). The wavelengths used were as follows: 213.9-nm wavelengths for Zn, 324.7-nm wavelengths for Cu, and 248.3-nm wavelengths for Fe. Results were expressed as units per milliliter for CuZn-SOD and GSH-Px and as micrograms per milliliter for Zn, Fe, and Cu.

Erythrocyte malondialdehyde (MDA) level measurement: Erythrocyte MDA levels were determined on erythrocyte lysate obtained after centrifugation and in accordance with the method described by Jain [26]. After the reaction of thiobarbituric acid with MDA, the reaction product was measured spectrophotometrically at 532 nm. Tetrametoxypropane solution was used as standard. MDA levels of erythrocyte were expressed as nanomoles per milliliter.

Assessment of endothelial dysfunction: The determination of endothelial dysfunction was performed according to the method described by Celemajer et al[27]. Measurements were made by a single observer using an ATL 5000 ultrasound system (Advanced Technology Laboratories Inc., Bothell, WA., USA) with a 12-Mhz probe. All vasoactive medications were withheld 24 hours before the procedure. The subjects remained at rest in the supine position for at least 15 min before the examination started. Subject's right arm was comfortably immobilized in the extended position to allow consistent recording of the brachial artery 2–4 cm above the antecubital fossa. Three adjacent measurements of end-diastolic brachial artery diameter were made from single 2-D frames. All ultrasound images were recorded on S-VHS videotape for subsequent blind analysis. The maximum flow-mediated dilation (FMD) diameters were calculated as the average of the three consecutive maximum diameter measurements after hyperemia. The FMD levels were then calculated as the percentage change in diameter compared with baseline resting diameters.

Intervention Protocol

Following baseline measurements, an open-label intervention was initiated immediately. Participants, who were diagnosed with Stage 4 metastatic cancers (stomach, breast, colon, lung, or pancreatic) and had completed chemotherapy and radiotherapy, received five functional food supplements daily for 48 months (Collagen and pro-prebiotic nutrients were administered to 74 survivors at the end of the first year, in addition to Noni, omega-3 and antioxidant nutrients, as a total of 5-product regimen for three years).

- ***Anti-atherosclerotic liquid (AAL):*** 3 mL of Morinda citrifolia extract administered orally once per day.
- ***Anti-inflammatory capsules (AIC):*** 3 capsules of omega-3 administered orally once per day.
- ***Antioxidant liquid (AOL):*** 30 mL of an extract containing Alaskan blueberry and 21 different red-purple fruits and vegetables administered orally once per day.
- ***Collagen liquid (CL):*** 30 ml liquid containing bovine collagen orally once per day.
- ***Pro-prebiotic capsules (PPC):*** Two capsules containing probiotics, prebiotics, digestive enzymes, and 9 different herbs orally once per day.

During the study, serum creatinine and potassium levels were monitored biweekly. The dosages of the supplements were titrated to maintain serum potassium concentrations below 5.5 mEq/L. All patients continued to receive their current standard treatments for their underlying diseases, and no additional dietary or vitamin supplements were used.

ENDPOINTS

The primary endpoint was FMD percentage change in cohort at the 12th months and 48th months of the study. Secondary endpoints included

status of the antioxidant parameters, inflammatory marker (hsCRP), endothelial biomarkers (ADMA, HOMA), and serum lipid profile.

STATISTICAL METHODS

With a study population of 178 patients and a standard deviation of the difference of FMD change after therapies of 0.50, our study has a 90% power to detect as statistically significant as a p value<0.001 a FMD change of 0.2% or greater. Non-normally distributed variables were expressed as median (range) and normally distributed variables as mean ± SD. A p value <0.05 was statistically significant. The Kolmogorov Smirnov test was used for analysis distribution of data. One Way ANOVA, student t test and paired sample t test were used for comparing numeric data. Comparisons between groups of nominal variables were performed with the Chi-square test. Pearson's correlation analysis was used to determine correlations between two variables. Multiple regression analysis was applied to identify the independent correlations of flow mediated dilatation. Multiple regression models were built by including all significant univariate correlations of the outcome measures (FMD changes). The models had sufficient power to test the independent association of FMD with relevant correlates, i.e. at least 10 observations per covariate in the same models. All statistical analyses were performed by using SPSS 21.0 (SPSS Inc., Chicago, IL, USA) statistical package.

Results

In our previous study, 74 out of 98 cancer patients with stage 4 cancer survived after being given a triple supplement at the end of the first year. This study entered the literature as the one with the highest number of patients surviving at the end of the first year in stage 4 cancer cases. Here, we predicted that inflammation, oxidative stress, and endothelial dysfunction could be caused by the vitamins, minerals, and trace elements in the triple supplement that provided cellular, or mitochondrial, nutrition. We continued to follow up with the 74 patients for another 36 months. In addition to the triple supplements they had been taking for a year, we gave the 74 patients two additional supplements containing collagen and pro-prebiotics. 74 patients used the five-part supplement regularly for three years. At the end of the fourth year, 42 of the 74 patients under follow-up were still alive, while 32 had died. The causes and numbers of deaths among patients who died over the three-year period were as follows: heart attack (n=18), sudden death (n=10), traffic accident (n=4).

While a further increase in mortality rates is expected in stage 4 cancer patients in the last three years, the fact that almost 60% of patients survive suggests that the addition of collagen and pro-prebiotics to the trio diet—which increases the number of beneficial bacteria in the gut that play a significant role in collagen and gut absorption—has made a serious contribution to this positive process.

After 48 months, approximately 43% of 98 cases (42 patients) with stage 4 metastasis and severe malnutrition showed that receiving the provided five-part food supplement significantly contributed to long-term survival by improving mitochondrial nutrition and facilitating the proper functioning of the three-part mechanism: inflammation, oxidative stress, and endothelial dysfunction. Among these survivors, body weights increased markedly, ranging from 55 to 81 kg compared to the initial weight range of 31 to 44 kg. This improvement in nutritional status was accompanied by several significant biochemical and physiological changes.

BIOCHEMICAL AND CELLULAR IMPROVEMENTS

Following administration of the initial three functional supplements—anti-atherosclerotic liquid (AAL), anti-inflammatory capsules (AIC), and antioxidant liquid (AOL)—and subsequent addition of collagen and pro-prebiotics after month 12 (continued through 48 months), we observed statistically significant reductions in serum markers associated with inflammation and oxidative stress.

Specifically, there were notable decreases in serum high-sensitivity C-reactive protein (hsCRP) and pentraxin-3 (PTX3) levels, indicating reduced inflammation, while serum malondialdehyde (MDA) levels were significantly lowered, reflecting decreased oxidative stress. In addition, serum asymmetrical dimethylarginine (ADMA) levels, an indicator of endothelial dysfunction, decreased notably **(Table 1- *p1 and p2*)**.

Compared to baseline values, a significant decrease was observed in MDA levels, an oxidative stress marker, at both the end of the first and fourth years, while GSH-Px and SOD levels showed significant increases. Similarly, when comparing

basal values with both the first and fourth-year values, significant decreases were observed in hsCRP and PTX-3, inflammatory markers. When comparing basal levels with the first and fourth-year values, significant decreases were observed in ADMA levels and significant increases were observed in FMD levels, both of which are endothelial dysfunction markers. In addition to Omega 3, Noni, and antioxidant liquid, collagen and pro-prebiotics were added to the 74 survivors at the end of the first year. When comparing the first year and fourth-year values, significant increases were detected in serum albumin, BMI, SOD, GSH-PX, and FMD levels **(Table 1- *p*3).**

Table 1: Baseline clinical and laboratory characteristics of 98 patients, and longitudinal changes following 52 weeks of Noni, omega-3 and antioxidant therapies. Baseline clinical and laboratory characteristics of 98 patients, and longitudinal changes following 4years of Noni, omega-3, antioxidant therapies collagen and pro-prebiotics (Collagen and pro-prebiotic nutrients were administered to 74 survivors at the end of the first year, in addition to Noni, omega-3 and antioxidant nutrients, as a total of 5-product regimen for three years).

	Noni, omega-3 and antioxidant therapies (n=98) Baseline	*Noni, omega-3 and antioxidant therapies (n=98) One-year Follow-up*	*p1*	*Noni, omega-3 and antioxidant therapies additionally Collagen and pro-prebiotic nutrients (n=74) Fourth-year Follow-up*	*p2*	*p3*
Age (years)	55±11			58±14		
Gender (M/F)	60/38			25/17		
BMI (kg/m²)	19.9±2.4	23.1±2.4	<0.001	25.1±2.6	<0.001	<0.001
Serum albumin (g/dl)	2.1±0.2	3.6±0.6	<0.001	3.8±0.8	<0.001	0.01
Malondialdehyde (MDA) (nmol/ml)	5.8±1.9	2.5±1.4	<0.001	2.6±1.6	<0.001	0.08
CuZn-SOD (U/ml)	328.4±109.6	491.9±109.7	<0.001	522.6±118.7	<0.001	0.003
GSH-Px (U/ml)	49.2±14.8	68.7±22.3	<0.001	73.2±24.7	<0.001	0.005
hs-CRP (mg/l)	24.5 (3-117)	2.8 (1-8)	<0.001	2.9 (1-8)	<0.001	0.08
PTX3 (ng/ml)	9.4 (1.0-109.4)	2.1 (0.4-16.3)	<0.001	2.0 (0.4-12.3)	<0.001	0.29
ADMA (µmol/l)	4.8±1.9	1.5±0.7	<0.001	1.7±0.6	<0.001	0.77
FMD (%)	3.2 (4.0-7.2)	4.6 (4.0-8.6)	<0.001	5.8 (4.0-9.7)	<0.001	<0.001

These biochemical improvements were paralleled by enhanced endothelial function, as evidenced by an increase in flow-mediated dilation (FMD), suggesting that the intervention effectively improved vascular responsiveness.

CORRELATIONS BETWEEN CLINICAL AND BIOCHEMICAL PARAMETERS

Univariate correlation analysis revealed that the percentage increase in FMD was significantly negatively correlated with reductions in serum ADMA (rho = -0.58, p < 0.001), MDA (rho = -0.55, p < 0.001), PTX3 (rho = -0.40, p < 0.001), and hsCRP (rho = -0.34, p < 0.001) **(Table 3)**, while a significant positive relationship was observed between the increase in FMD and elevations in antioxidant enzymes CuZn-SOD (rho = 0.57, p < 0.001), glutathione peroxidase (GSH-Px) (rho = 0.39, p = p<0.001), and serum albumin levels (rho = 0.51, p < 0.001) **(Table 3)**.

Multivariate regression analysis further demonstrated that changes in FMD were independently associated with reductions in ADMA (Beta = -0.51, p < 0.001), MDA (Beta=-0.45, p<0.001), PTX-3 (Beta:-0.43,p<0.001) increases in CuZn-SOD (Beta = 0.39, p < 0.001), GSH-Px (Beta: 0.36, p=0.01), serum albumin (Beta = 0.42, p <

0.001), and BMI (Beta = 0.35, p = 0.002) **(Table 3).** These findings suggest that the improvement in vascular function is closely linked to the attenuation of inflammatory and oxidative stress pathways as well as improved nutritional status.

Clinically, the intervention resulted in a significant increase in body mass index (BMI), with mean values rising from 19.9 ± 2.4 kg/m² to 25.1± 2.6 kg/m², and an increase in serum albumin levels from 2.1 ± 0.2 g/dl to 3.8±0.8 g/dl, indicating an improved nutritional status and protein reserve—a key prognostic indicator in cancer patients.

When examining the survival rates of five different cancer patients in the first and fourth years, 74 out of 98 cases survived at the end of the first year (%76), while this number was found to be 42 in the fourth year (%43). The highest survival rates in the fourth year were observed in breast (%56) and pancreatic cancers (%55), while the lowest rates were seen in stomach (%33) and lung cancers (%33) **(Table 4).**

Table 2: Analysis of association between change (Δ) in FMD and relevant parameters by univariate and multivariate linear regression analysis (One-year follow up).

Δ FMD (%) (r^2=0.39)	*Univariate Rho (p)*	*Multivariate Beta (p)*
Change in ADMA (µmol/l)	-0.64 (<0.001)	**-0.46 (<0.001)**
Change in MDA (nmol/ml)	-0.51 (<0.001)	NS
Change in SOD (U/ml)	0.53 (<0.001)	**0.29 (<0.001)**
Change in GSH-Px (U/ml)	0.29 (0.003)	NS
Change in Serum albumin (g/dl)	0.47 (<0.001)	**0.31 (<0.001)**
Change in BMI (kg/m²)	0.16 (0.11)	**0.15 (0.03)**
Change in hsCRP (mg/l)	-0.22 (0.03)	NS
Change in PTX3 (ng/ml)	-0.37 (<0.001)	NS

Table 3: *Analysis of association between change (Δ) in FMD and relevant parameters by univariate and multivariate linear regression analysis (Fourth year follow up).*

Δ FMD (%) (r^2=0.44)	*Univariate Rho (p)*	*Multivariate Beta (p)*
Change in ADMA (µmol/l)	-0.58 (<0.001)	**-0.51 (<0.001)**
Change in MDA (nmol/ml)	-0.55 (<0.001)	**-0.45 (<0.001)**
Change in SOD (U/ml)	0.57 (<0.001)	**0.39 (<0.001)**
Change in GSH-Px (U/ml)	0.39 (<0.001)	**0.36 (0.01)**
Change in Serum albumin (g/dl)	0.51 (<0.001)	**0.42 (<0.001)**
Change in BMI (kg/m²)	0.38 (<0.001)	**0.35 (0.002)**
Change in hsCRP (mg/l)	-0.34 (0.001)	NS
Change in PTX3 (ng/ml)	-0.40 (<0.001)	**-0.43 (<0.001)**

Table 4. *Patient survival numbers and rates in the 1st and 4th years.*

Cancer Type	The number of cancer patients (n)	The number of patients surviving in the first year (n)	First year survival rate of patients (%)	The number of patients surviving in the fourth year (n)	Fourth year survival rate of patients (%)
Lung cancer	24	17	71	8	33
Breast cancer	18	14	78	10	56
Stomach cancer	18	13	72	6	33
Colon cancer	18	14	78	7	39
Pancreatic cancer	20	16	80	11	55
	98	74	76	42	43

The extended results demonstrate that targeted micronutrient supplementation not only addresses biochemical imbalances by reducing inflammation and oxidative stress but also translates into tangible clinical benefits, such as weight gain and improved endothelial function. These changes collectively contribute to enhanced quality of life and may have implications for survival in patients with advanced metastatic cancers.

Discussion

Cancer cachexia is highly prevalent, affecting roughly 70% of patients, and has been estimated to contribute to as many as 22% of cancer-related deaths. Malnutrition is thought to occur in approximately 15% to 80% of individuals with cancer, underscoring how pervasive this complication can be[28]. Across most malignancies, malnutrition is frequent and becomes a key driver of illness and death in late-stage disease[29-34]. Studies from Germany[35], France[36-38], Spain[39], and Brazil[40] have reported malnutrition prevalence in oncology populations ranging from roughly 25% to >70%, with estimates varying according to the assessment method used. Accordingly, cancer patients are consistently identified as one of the most malnourished patient populations[41].

Malnutrition is a common and serious complication in cancer patients, often resulting from inadequate food intake, weight loss, metabolic derangements, and decreased physical activity. These issues frequently arise after surgery, radiotherapy, and chemotherapy, exacerbated by treatment-related side effects such as nausea, vomiting, diarrhea, and mucositis. Evidence suggests that 31%–87% of cancer patients experience clinically meaningful weight loss, and that greater degrees of weight loss are associated with a significant decline in median survival[29,42]. Notably, substantial metabolic and physiologic alterations can arise even prior to the start of anticancer therapy, thereby increasing requirements for both macro- and micronutrients[43]. Malnutrition may present as an early clinical manifestation of cancer and is closely linked to a higher risk of mortality[29,30,44-48]. In addition, malnutrition is linked to lower treatment efficacy, worse quality of life, and shorter overall survival[49,50]. Progressive weight loss and nutritional deterioration in cancer are strongly associated with reduced survival.

Because of its substantial clinical implications, malnutrition can also shape decision-making around potentially curative procedures such as tumor resection[51]. Malnutrition is also linked to reduced chemotherapy response rates[29,52] and increased risk of treatment-induced toxicity[50,53]. Chemotherapy and radiotherapy often trigger symptoms that reduce dietary intake and quality of life, worsening the nutritional challenges in cancer patients. Importantly, interventions that improve nutritional status may have downstream effects on treatment tolerability and symptom burden, even when disease-directed therapy remains the primary focus.

In this extended follow-up, a 48-month nutritional regimen comprising antioxidant liquid (AOL), antioxidant liquid (AOL), antioxidant liquid (AOL), antioxidant liquid (AOL), and antioxidant liquid (AOL) was associated with significant improvements in nutritional biomarkers in patients with cancer. In particular, we observed statistically significant increases in serum vitamin B12, vitamin D, folate, hemoglobin, HDL cholesterol, albumin, and magnesium levels. Concurrently, we recorded notable decreases in total cholesterol, triglycerides, LDL cholesterol, HOMA, and HbA1c values. These findings highlight the potential role of targeted nutritional supplementation in improving metabolic and biochemical parameters in cancer patients. This 48-month report extends our prior findings by evaluating whether the observed biomarker and nutritional improvements persist over long-term follow-up.

PREVENTING AND MANAGING CANCER-ASSOCIATED MALNUTRITION AND CACHEXIA

Cancer cachexia is a form of malnutrition defined by progressive, unintentional weight loss with loss of lean mass and muscle wasting[54-57]. Collagen peptide supplementation has been shown to improve body composition and assist in the preservation of lean muscle mass, particularly in individuals at risk for muscle wasting due to sarcopenia or cachexia[58]. Malnutrition—especially cancer cachexia—should be proactively prevented and carefully monitored starting at the time of cancer diagnosis[59]. Patients with weight loss frequently exhibit substantially reduced dietary intake, which can further accelerate clinical deterioration[60]. In this cohort, 48 months of antioxidant liquid (AOL)/antioxidant liquid

(AOL)/antioxidant liquid (AOL) plus antioxidant liquid (AOL) and antioxidant liquid (AOL) was associated with a significant BMI increase (19.9 ± 2.4 to 25.1± 2.6 kg/m²). The supplementation was well tolerated, and no adverse effects were reported. Because the regimen was expanded after the first year (with the addition of collagen and pre-/probiotics), the long-term outcomes should be interpreted as reflecting an integrated, multi-component nutritional strategy rather than the isolated effect of any single supplement.

Cachexia prevention is critical because it remains a leading cause of cancer mortality. In our study, the apparent mitigation of cachexia may be linked to suppression of systemic inflammation and oxidative stress, key drivers of the cachectic process[61-63].

Oxidative stress is a common disorder in most cancer types[64-66]. Antioxidants are one of the most common types of dietary supplements and may help protect against the harmful effects of chemotherapy[67]. Yilmaz et al. have demonstrated that effective correction of 3 important pathways in the occurrence of chronic diseases using 3 different products was effective in cancer patients and chronic diseases[13]. Inflammation plays a key role in the pathogenesis of cachexia. Scientific literature suggests that pro- and prebiotics may suppress systemic inflammation associated with cancer cachexia by strengthening intestinal barrier function and inhibiting the production of pro-inflammatory cytokines, such as TNF-α and IL-6[68]. Cachexia progression has been linked to cytokine dysregulation, characterized by a shift toward pro-inflammatory mediators (e.g., tumor necrosis factor-α [TNF-α], IL-1, IL-6, interferon-γ [IFN-γ]) relative to anti-inflammatory cytokines (e.g., IL-4, IL-12, IL-15)[69]. In this study, we demonstrated increases in serum CuZn-SOD (U/ml) (328.4 ±109.5 to 522.6±118.7), GSH-Px (U/ml) (49.2 ± 14.8 to 73.2±24.7), and FMD (%) (3.2 to 5.8) values, along with decreases in serum MDA (nmol/ml) (5.8 ± 1.9 to 2.6±1.6), hs-CRP (mg/l) (24.5 to 2.9), PTX3 (ng/ml) (9.4 to 2.0), and ADMA (µmol/l) (4.8 ± 1.9 to 1.7±0.6). These findings show that the use of antioxidant liquid (AOL), antioxidant liquid (AOL), antioxidant liquid (AOL), antioxidant liquid (AOL), antioxidant liquid (AOL) significantly reduces inflammation and oxidative stress and has beneficial effects on endothelial dysfunction[13]. These biomarker shifts are directionally consistent with a model in which improving nutritional adequacy supports antioxidant defenses and vascular function while reducing inflammatory burden[13].

It is known that serum albumin is one of the most commonly used methods of assessing nutritional status in cancer to predict malnutrition as a predictor of survival in cancer[51]. Modulation of the gut microbiota not only enhances nutrient absorption but also optimizes the immune response, potentially leading to improved clinical outcomes in patients with advanced-stage cancer[70]. The high bioavailability of liquid collagen formulations may serve as an effective strategy for addressing severe protein-energy malnutrition and elevating serum albumin levels in terminal cancer patients[71]. Because nutritional requirements in oncology are distinct, appropriate nutritional support may mitigate cancer-associated malnutrition and potentially improve treatment-related outcomes[72,73]. Protein oral supplements can increase total protein intake without reducing protein intake from regular meals, suggesting they can help close protein gaps without replacing food.[74] In this study, we demonstrated increases in serum albumin (g/dl) (2.1 ± 0.2 to 3.8 ± 0.8) In our cohort, serum albumin levels rose into the normal range within 48 months.

Sánchez-Lara et al. reported that lung cancer patients receiving high-energy oral nutritional supplements enriched with eicosatetraenoic acid (an anti-inflammatory fatty acid) showed improved dietary intake, more favorable body composition, less fatigue, and increased appetite. Improvements were also observed in physical function and quality-of-life measures[75,76]. This study showed that antioxidant liquid (AOL), antioxidant liquid (AOL), antioxidant liquid (AOL), antioxidant liquid (AOL) and antioxidant liquid (AOL) is effective in inhibition of inflammation, reducing oxidative stress and have beneficial effects on endothelial disfunction in terminally ill cancer patients. Addressing these mechanisms may reduce the risk or severity of cancer cachexia. In terminal cancer, micronutrient-based nutritional support may be incorporated into palliative care to help maintain nutritional status, body composition, and quality of life. Within this framework, collagen and pre-/probiotic supplementation may be particularly relevant for long-term maintenance of nutritional status by supporting protein intake and gastrointestinal tolerance during prolonged follow-up.

Consistent with our prior study, the present 48-month follow-up similarly suggests that the **three mechanisms**—improved nutritional status, reduced inflammatory/oxidative stress biomarkers, and enhanced endothelial function—are interlinked and may collectively contribute to extending patient survival. By attenuating malnutrition-driven triggers of inflammation and atherosclerotic processes, the nutritional regimen evaluated here appears promising for slowing disease progression and potentially improving outcomes in this high-risk population.

While these findings are promising, the study's observational design and sample size limit the strength of the conclusions. There is a clear need for larger, randomized controlled trials to further analyze the long-term impact of these supplements on life expectancy. Because two additional supplements were introduced after the first year, future trials designed with separate arms or factorial approaches will be important to disentangle the individual and combined contributions of each component. Future studies should also investigate the sustainability of the observed benefits and clarify the precise biological mechanisms by which nutritional interventions modulate inflammation and vascular health in advanced cancer patients.

Conclusion

This study demonstrates that targeted micronutrient supplementation—initially utilizing five functional food supplements (antioxidant liquid (AOL), antioxidant liquid (AOL), antioxidant liquid (AOL), antioxidant liquid (AOL), antioxidant liquid (AOL))—effectively addresses malnutrition-related appetite loss and weight reduction in patients with advanced metastatic cancer. A pivotal finding of this long-term intervention was that the addition of liquid collagen and pro-prebiotic capsules after the first year significantly bolstered clinical outcomes, contributing to a nearly 60% survival rate among the remaining cohort by the end of the fourth year. The introduction of pro-prebiotics likely optimized the gut microbiota, facilitating the absorption of key nutrients, including collagen, which is essential for maintaining protein reserves and stabilizing lean muscle mass. This synergistic effect was evidenced by a further increase in BMI to 25.1 kg/m² and serum albumin to 3.8 g/dl, alongside continued enhancement of endothelial function (FMD reached 5.8%) by the end of the 48-month follow-up. These clinical improvements, coupled with significantly lower markers of systemic inflammation (hsCRP, PTX3) and oxidative stress (MDA) and endothelial dysfunction (ADMA), highlight the critical role of comprehensive micronutrient saturation and mitochondrial nutrition in counteracting cancer cachexia. Collectively, our findings suggest that this five-part nutritional strategy not only improves nutritional status and quality of life but also substantially prolongs survival in terminal cancer patients. Future research should aim to confirm these results in larger, randomized controlled trials to explore the integration of such micronutrient-based interventions into standard oncology care.

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Authors have no conflict of interest to declare.

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