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Original Article

The Effects of Protein Support With Various Content On Nutrition Status and Clinical Outcomes in Elderly Malnourished Cancer Patients

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Abstract

Aim: The aim of this study was to investigate the nutritional status and clinical outcomes of elderly malnourished cancer patients receiving oral or enteral nutrition with various protein content. *Methods:* This retrospective study included 19 cancer patients receiving the β-hydroxy-β-methyl butyrate (HMB) + glutamine (GLN) + arginine (ARG) (1st group) combination, 48 receiving only GLN content (2nd group) and 19 receiving standard enteral supplementation (3rd group). The nutritional status of the patients was analyzed by nutritional risk screening (NRS-2002). Anthropometric measurement was taken and the biochemical parameters were analyzed. All measurements were recorded twice, before and after nutrition therapy. *Results:* The hospital mortality rate was 7% (n=6) among all patients, and our two-year follow-up mortality rate was 36% (n=31). We observed no differences between the groups in the length of hospital stay, nutrition therapy duration and mortality (p>0.05). The mean NRS-2002 score was found to be statistically significantly different between the control and glutamine groups after nutrition therapy with lower scores in the glutamine group (p=0.001). Post-nutrition serum albumin levels were also higher in the glutamine group than in the control group (p=0.001). *Conclusion:* We observed that patients who received standard enteral nutrition had higher NRS-2002 scores and lower serum albumin levels compared to patients who receiving only GLN or HMB combination. We were unable to find a factor that could be a good predictor of survival. Other randomly controlled studies are needed to determine the effectiveness of HMB or only GLN use in cancer patients.

Clinical Relevancy Statement

Cancer is among the leading causes of morbidity and mortality worldwide, and the number of new cases is expected to rise significantly over the next few decades. Inadequate nutritional intake is observed frequently in these patients and is associated with weight loss, which may especially be severe in elderly. Important findings of this study include a high incidence of malnutrition in the pre-nutritional period and a low NRS-2002 score following glutamine-supported nutrition therapy and these findings are clinically relevant.

Introduction

According to the National Cancer Institute (NCI), cancer is a collection of related diseases. Some of the body's cells begin to divide in an uncontrolled manner and spread into surrounding tissues in this condition.[1] Cancer is among the leading causes of morbidity and mortality worldwide, and the number of new cases is expected to rise significantly over the next decade.[2] According to the latest WHO data from 2018, the cancer incidence in Turkey is 225.1 / 100.000. It is estimated that the number of new cancer cases will increase by 70% and reach 22 million in 20 years.[3] At the same time, all types of cancer treatment such as surgery, radiation therapy, and pharmacological therapies are becoming more sophisticated, precise

and powerful, and can target specific characteristics of individual cancers. It is therefore now possible to convert some cancers to chronic diseases even if a cure is not available. However, all these treatments are impeded or precluded by the frequent development of malnutrition and metabolic derangements in cancer patients, induced either by the tumour or its treatment.[2]

Unlike simple malnutrition, the negative energy balance and skeletal muscle loss observed in cancer patients is driven by a combination of reduced food intake and metabolic derangements (e.g. elevated resting metabolic rate, insulin resistance, lipolysis, and proteolysis, all of which aggravate weight loss and are provoked by systemic inflammation and catabolic factors) that can be host- or tumour-derived. Cancer-associated malnutrition can therefore only be partially reversed by conventional nutritional support.[2,4,5] Artificial enteral feeding may stabilize the nutritional status inn cancer patients who are unable to eat, digest or absorb food.[2]

Although weight loss is associated with mortality and morbidity, there is no study showing an inverse relationship between the use of enteral or parenteral nutrition and the occurrence of cachexia in the literature. The most effective nutritional therapy for cancer patients is therefore unknown.[4] However, it has been shown that formulas enriched with glutamine and other immunomodulatory agents can have positive effects on the nutritional status of cancer patients under perioperative conditions.[6]

Current studies report the three nutritional substrates that affect muscle proteolysis as β-hydroxy-β-methylbutyrate (HMB), glutamine (GLN) and arginine (ARG).[4-7] All three of these nutrients have been shown to impact the loss of muscle or slow the turnover of muscle protein. Glutamine plays an important role in the nutrition of lymphocytes and intestinal mucosa. Maintenance of high intracellular levels of glutamine in the muscle appears to be a major regulator of muscle proteolysis. Arginine is the precursor to nitric oxide, which is thought to play a role in nitrogen sparing in trauma, wound healing, and immune stimulation. Finally, HMB is believed to exert a protective effect on muscle, minimizing the processes causing muscle damage and proteolysis. HMB supplementation has been shown to markedly decrease exercise-induced muscle damage. The mechanism by which HMB slows down muscle protein breakdown is not fully understood but HMB likely acts on muscle by mechanism(s) that are distinct from those of arginine and glutamine[7].

This study was planned to investigate the nutritional status and clinical outcomes of elderly malnourished cancer patients receiving oral or enteral nutrition with various protein content.

METHODS

This retrospective study included geriatric cancer patients aged 60 to 76 years who had been admitted to the '[removed for blind peer review]' University's Medical Sciences Hospital in a 2- year period and required nutritional intervention via oral nutrition replacement or enteral nutrition (through the nasogastric or nasoenteral routes, gastrostomy or jejenostomy) for over 5 days. Exclusion criteria were feeding initiation by the parenteral route, intravenous glutamine use, feeding duration <5 days, inability to achieve nutritional goals (caloric and protein requirements), and impossibility of performing an anthropometric evaluation. Patients with systemic diseases such as diabetes mellitus, hypertension, renal insufficiency and cancer stage 4 were also excluded from the study. The study was approved by the Research Ethics Committee of the '[removed for blind peer review]' University (No: 80706068.02-050/E4) and informed consent was obtained from all participants.

Assessments

The patients' general information was obtained retrospectively from the patient follow-up forms. Age, gender, diagnosis, operation status, length of hospital stay, and duration of nutrition therapy was recorded. Patients with systemic disease were eliminated. The discharge, death and referral status information was also obtained from the patient follow-up forms. The survival or death status of the patients was recorded using the hospital's electronic patient information system software. Patient information such as type and

stage of cancer, chemotherapy (CT) and/or radiotherapy (RT), metastasis status, and type of metastasis were retrieved from the hospital's electronic patient information system or the oncology doctors that were consulted.

Nutritional Assessments

The patients were evaluated by a Nutrition Committee (NC) composed of physicians, dietitians and nurses that provided nutritional assessments, recommendations and consultations for inpatients who required nutritional support during their hospital stay. All the patients were followed-up during their hospitalization until discharge or in-hospital death. Clinical and nutritional practice data (administration route, infusion method, energy and protein requirements, prescription, type of enteral formula, energy and protein target, milliliters administered and nutritional adequacy), nutrition-related complications, gastrointestinal complications, and causes of EN discontinuation were assessed by the NC every day during clinical visits.

Patients were classified into 3 groups according to their EN formula with different protein types: (1) Enteral nutrition formula with a combination of HMB, GLN and ARG, (2) enteral formula with only GLN, (3) standard enteral formula. Group 1 (n = 19) consumed one sachet (24 g) of enteral formula powder (containing 1.3 g HMB, 7.4 g L-arginine and 7.4 g L-glutamine) (Abound; Ensure, Abbott Laboratories, the Netherlands) in about 30 minutes after mixing it with 250-300 ml of drinking water, 2 times a day. Group 2 (n = 48) consumed one sachet (containing 5 g of L-glutamine) of enteral formula powder in approximately 250-300 mL of drinking water in about 30 minutes after mixing, 6 times a day (30 g L-Glutamine) (Resource Glutamine; Nestle Laboratories, Switzerland). The patients in the second group received these mixtures through oral and/or tube feeding. Group 3 (n = 19) was the control group and received a standard enteral formula without HMB, GLN or ARG (Standard; Ensure, Abbott Laboratories, the Netherlands).

The patients' resting energy expenditure was calculated using the Harris–Benedict equation and adjusted for sedentary activity (1.2 g/kg/day) and also for body temperature by adding 1% for every 0.1°C above 37°C (7). The daily target protein requirement was calculated as 1.2-1.5g/kg. The defined protein target was adapted based on certain clinical conditions (e.g. renal and hepatic insufficiency).[8,9] The food consumption of the patients in the hospital was recorded daily and the adequacy of energy intake was evaluated. In case of insufficient energy intake, the required energy was provided with an enteral formula.

Anthropometric Measurements

Each patient's body weight was measured with a scale. Height was measured with a stadiometer with the feet joined and in the Frankfurt plane. [8] The mid-upper arm circumference (MUAC) was measured at the midpoint of the non-dominant arm with a measuring tape. The body mass index (BMI) was calculated as weight (kg) divided by height (m) squared. All anthropometric measurements were performed by the NC nurse. BMI measurements were evaluated according to the National Center Health Statistics (NCHS) reference values. MUAC measurements of the patients were evaluated according to the reference values of the National Nutrition and Health Survey-1 (NHANES-1).[10]

Malnutrition was assessed using Nutritional Risk Screening (NRS-2002). The patients with an NRS-2002 score of 3 or more were accepted as under high nutritional risk.[11] Nutrition status was assessed within the first 24 hours after consultation and weekly during hospitalization.

Laboratory Parameters

Laboratory analyses were performed at the hospital's Biochemistry Laboratory. Biochemical parameters included fasting blood glucose, total protein, albumin, haematological parameters [serum haemoglobin (Hb), haematocrit (Hct) (%), serum leukocyte (WBC), erythrocyte (RBC), % lymphocyte (%)], C-reactive protein (CRP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), urea and creatine.

Outcomes

Anthropometric measurements, NRS-2002 scores and blood samples were recorded twice from each patient, before and after nutrition therapy. Clinical outcome was assessed with nutritional status, clinical complications, and hospital and 2-year follow-up mortality rates. Patient mortality was followed from the hospital electronic software until 2015 after the patient's discharge from the hospital. Clinical complications were assessed in terms of enteral problems (aspiration, gastric residue, vomiting, diarrhea, abdominal distension, intolerance to feeding).

Statistical Analysis

All statistical analyses were performed using the SPSS software (ver. 16.0; SPSS, Inc., Chicago, IL, USA). A p value <0.05 was deemed to indicate statistical significance. Simple descriptive statistics were used for demographic analyses. One-way ANOVA or non-parametric Kruskal-Wallis analyses was used for 3 or more group differences of continuous measurements. Continuous values were compared between two independent groups with Student's t test or the unpaired t test. The Mann-Whitney U test was performed to test the significance of pairwise differences using Bonferroni correction to adjust for multiple comparisons. An overall 5% type-1 error level was used to infer statistical significance. Proportions were compared with the $\chi 2$ test. Correlation analysis was used to determine the relationship between continuous measurements. Logistic regression analysis was employed to identify independent factors that affected mortality.

Results

A total of 414 elderly cancer patients who required nutritional support during hospitalization for their illness were considered eligible and the data from 86 patients were analyzed (Figure 1). All patients were

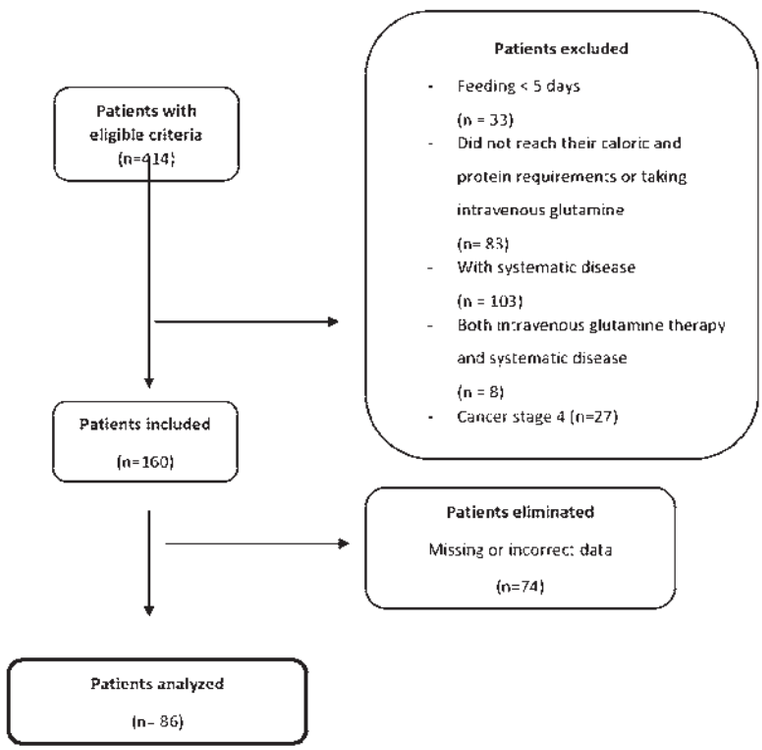

Figure 1. Nutritional support flow chart. Eligible criteria were, geriatric cancer patients at least 60 years and under 75 years of age who required nutrition intervention (n=414). 234 patients excluded and 86 patients analyzed.

classified as suffering from malnutrition according to NRS-2002 at the beginning of the study. Baseline characteristics are presented in Table 1. There was a relatively high percentage of lung (29.1%) and haematological (26.7%) cancer cases. No stage classification was performed in patients with haematological cancer. None of the patients had metastases. The hospital mortality rate was 7% (n=6) and our two-year mortality rate was 36% (n=31) for all patients. The nutrition therapy complication rate was 9.3% (n=8). In patients who received z therapy, 5.8% (n=5) had nausea and vomiting, 1.2% (n=1) diarrhea and 2.3% (n=2) distention. We observed no differences in the length of hospital stay, nutrition therapy time and mortality between the groups (p>0.05). The anthropometric measurements, NRS-2002 score and biochemical parameters of the patients are presented in Table 2. The changes in anthropometric measurements (body weight, BMI, and MUAC) of the patients during nutrition therapy were not statistically significant (p> 0.05) in any of the three groups. There was no significant difference in mean NRS-2002 scores measured within the first 48 hours after hospitalization between the groups (p> 0.05). However, the mean NRS-2002 score was found to be different between the groups after nutrition therapy (p=0.004) with a significant difference between the control and glutamine groups (Bonferroni corrected *p*-value =0.001). The mean NRS-2002 score after nutrition therapy was lower in the glutamine group than the control group. The mean NRS-2002 score was found to be decreased after nutrition therapy in Group 2 (p = 0.001) (Table 2).

Regarding biochemical parameters, only the final serum albumin levels were statistically significantly different between the groups (p=0.04). The difference between the control and glutamine groups was found to be significant (Bonferroni corrected *p*-value =0.001) with the mean serum albumin levels higher in the glutamine group than the control group (p=0.001). The changes in biochemical parameters after nutrition therapy were significant in serum albumin (p=0.001), total protein (p=0.003) and lymphocyte (p=0.001) mean levels in group 2. At the end of the study period, albumin mean values decreased in all patients who had a higher NRS-2002 score (p=0.001) (Figure 2).

Logistic regression analysis showed that cancer type, tumour stage, and final serum protein levels were significant factors among the variables predicting hospital mortality. Similarly, enteral protein support with various content, final serum protein, albumin and CRP levels were found to be significant among the variables predicting two-year mortality (Table 3).

Discussion

All the patients included in the study were malnourished according to NRS-2002. Malnutrition can affect both the prognosis and outcome and cancer patients need to be maintained in a good nutritional state to increase the beneficial effects of anticancer therapy, sustain the ability to confront stress, and minimize the side effects of treatment. In this respect, nutritional screening of hospitalized cancer patients is the most important step in preventing malnutrition development.[12] Two main evaluation processes exist to identify patients with or at risk of malnutrition: nutritional screening and nutritional assessment. Although no standardized nutritional screening tool has been designed specifically for use in cancer patients, several tools exist and have been shown to be effective in different patient groups such as primary care patients, hospital inpatients and the elderly.[13] Nutritional status was assessed on the basis of the Nutrition Risk Score (NRS 2002) in a large cohort (n = 1453) of cancer outpatients and 32% were found to have nutritional risk.[14] We found post-nutrition albumin levels to decrease with higher NRS-2002 scores in this study and therefore believe that it is necessary to follow the patient's nutritional status during hospitalization, especially in elderly cancer patients.

Glutamine is the most abundant amino acid in the body and constitutes 61% of the total pool of amino acids in the human muscle.[15] It is the most important circulating "nitrogen shuttle" accounting for 30% to 35% of all amino acid nitrogen transported in the blood[16] and also serves as important precursor for the *de novo* synthesis of nucleotides, nucleic acids, amino sugars, proteins, and glutathione. Glutamine is a preferred respiratory fuel for rapidly proliferating cells such as enterocytes and lymphocytes.[16] The hyper

Table 1. Patient characteristics

Characteristics	Group 1 (n = 19)	Group 2 (n = 48)	Group 3 (n = 19)	p
Age ±SD), years	69.00±4.38	66.5±4.55	68.21±5.74	n.s.
Sex (male/female), n	11/8	34/14	11/8	n.s.
Cancer type, n(%)				
Haematological	1(5.26)	15(31.2)	7(36.8)	
Gastrointestinal	8(42.1)	7(14.5)	4(21.1)	
Lung	4(21.1)	18(37.5)	3(15.7)	
Oral cavity	4(21.1)	4(8.3)	2(10.5)	
Head-neck	–	1(2.1)	–	
Genitourinary	1(5.26)	1(2.1)	2(10.5)	
Brain	–	1(2.1)	1(5.26)	
Breast	1(5.26)	–	–	
Skin	–	–	–	
Parotid gland	–	1(2.1)	–	
Tumour stage, n (%)				
Haematological	–	11(22.9)	7(36.8)	0.02
pT1	1(5.26)	3(6.25)	1(5.26)	
pT2	4(21.1)	17(35.4)	7(36.8)	
pT3	14(73.68)	17(35.4)	4(21.1)	
Adjuvant therapy, n(%)				
Chemotherapy (CT)	8(42.1)	22(45.8)	9(47.36)	n.s.
Radiation therapy (RT)	2(10.5)	2(4.16)	–	
None	8(42.1)	20(0.41)	8(42.1)	
Combined (CT+RT)	1(5.26)	4(8.3)	2(10.5)	
Surgery status, n (%)	13	20	7	n.s.
NRS-2002 score, baseline ±SD)	4.63±0.83	4.46±0.71	4.53±0.77	n.s.
Type of nutrition therapy, n (%)				
Oral replacement therapy	17	35	17	n.s.
Enteral therapy	2	13	2	
Nutrition therapy time ±SD)	10.42±5.73	13.81±8.74	15.16±10.54	n.s.
Length of hospital stay ±SD)	17.05±10.05	16.02±10.12	18.84±13.24	n.s.
Hospital mortality, n (%)	–	45	16	n.s.
2-year follow-up mortality, n (%)	6	18	7	n.s.

Abbreviations: NRS-2002; Nutritional risk screening; n.s.; not significant

Table 2. Mean patient anthropometric measurement, NRS-2002 score and biochemical parameter values during nutrition therapy by group

Value	Group 1 (n=19)	Group 2 (n=48)	Group 3 (n=19)	p
BMI (kg/m²), mean (SD)				
Baseline	23.65±3.89	22.44±4.32	23.38±3.49	n.s.
Final	23.64±3.93	22.66±4.27	23.12±3.36	n.s.
MUAC (cm), mean (SD)				
Baseline	25.36±3.09	26.87±2.71	25.68±3.89	n.s.
Final	25.52±2.85	27.12±2.58	25.37±4.03	n.s.
NRS-2002 score, mean (SD)				
Baseline	4.63±0.83	4.46±0.71	4.52±0.77	n.s.
Final	4.32±0.96	4.08±0.92[a**]	5.05±1.08	0.004[b**]
Albumin (g/dL), mean (SD)				
Baseline	2.83±0.59	2.77±3.05	2.91±0.57	n.s.
Final	2.77±0.45	3.03±0.46[a**]	2.75±0.51	0.04[b*]
Total protein (g/dL), mean (SD)				
Baseline	6.44±0.82	5.55±0.61	5.83±1.02	n.s.
Final	5.69±0.63	6.05±0.87[a**]	5.61±0.88	n.s.
CRP, mean (SD)				
Baseline	62.83±27.96	97.39±62.09	74.62±54.66	n.s.
Final	46.43±38.61	55.34±45.59	80.78±55.42	n.s.
Lymphocyte (/mm), mean (SD)				
Baseline	1344.04±563.13	875.16±645.31	898.93±211.88	n.s.
Final	1604.±847.28	1209.08±834.65[a**]	732.29±172.60	n.s.
Urea (mg/dL), mean (SD)				
Baseline	29.42±12.45	35.82±15.64	27.90±6.40	n.s.
Final	37.08±26.18	42.18±23.42	34.09±7.82	n.s.
Creatine (mg/dL), mean (SD)				
Baseline	0.64±0.15	0.75±0.26	0.71±0.32	n.s.
Final	0.70±0.27	0.72±0.23	0.78±0.39	n.s.
AST (U/L), mean (SD)				
Baseline	25.42±17.69	29.59±20.52	35.59±21.53	n.s.
Final	30.14±25.0	28.78±20.86	38.42±29.49	n.s.
ALT (U/L), mean (SD)				
Baseline	18.06±8.03	21.94±13.99	27.81±21.06	n.s.
Final	24.67±15.79	26.59±21.24	41.02±41.93	n.s.
Glucose (mg/dL), mean (SD)				
Baseline	97.34±23.00	105.25±19.29	104.49±24.93	n.s.
Final	101.38±17.66	110.03±18.14	108.46±20.22	n.s.

Abbreviations: BMI; Body mass index, MUAC; Mid upper arm circumference, NRS-2002; Nutritional risk screening; Group 1: combined HMB, glutamine, arginine, Group 2: only glutamine, Group 3: control; [a]Paired sample t-test or non-parametric Wilcoxon Signed Rank test*p<0.05, **p<0.001; [b]One-way analysis or non-parametric Kruskal-Wallis analyses*p<0.05, **p<0.001, n.s.; not significant

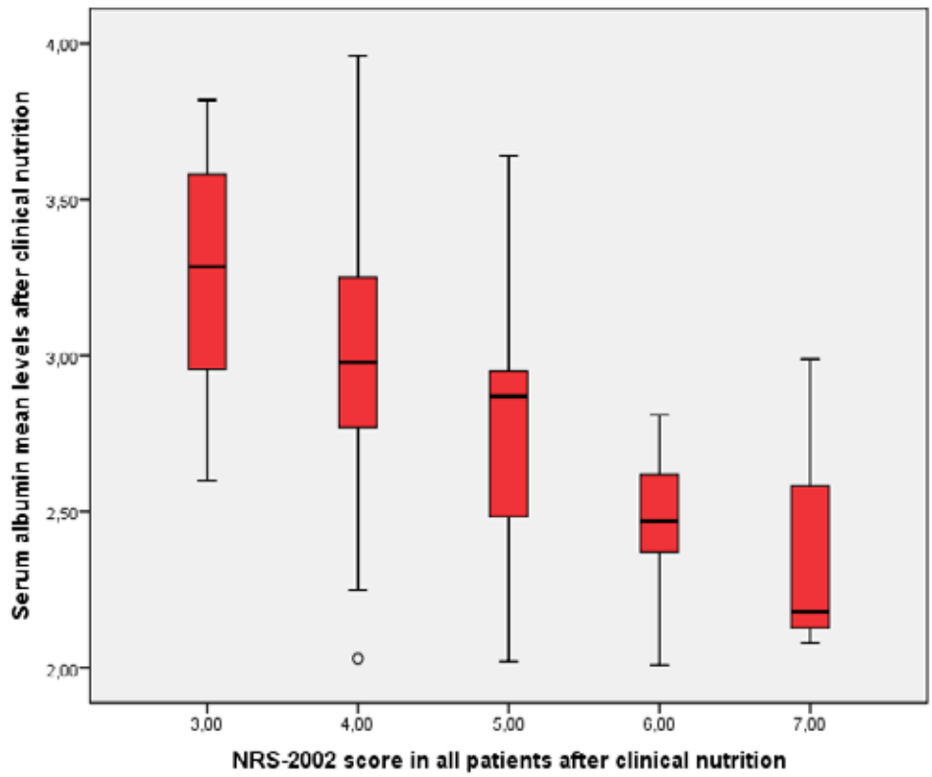

Figure 2. Relationship between serum albumin levels and NRS-2002 score after nutrition

Table 3. Variables predicting mortality and follow-up mortality

Mortality (R squared=0.37, p=0.02*)		2-year mortality (R squared= 0.46, p=0.01*)	
Variable	**p**	Variable	**p**
Groups	0.62	Age	0.15
Cancer type	0.04*	Gender	0.18
Tumour stage	0.01*	Groups	0.02*
Final serum albumin levels	0.64	Cancer type	0.34
Final serum protein levels	0.06*	Final serum protein levels	0.04*
Final serum CRP levels	0.12	Final serum albumin levels	0.03*
Final NRS-2002 score	0.35	Final serum CRP levels	0.01*
		Final NRS-2002 score	0.07
		Complications	0.15

* Significantly different, p<0.05

catabolic state during cancer is a hyper inflammatory cytokine release pattern combined with insufficient endogenous availability of glutamine due to increased consumption. Overall glutamine deprivation is associated with depression, reduced protein synthesis, muscle loss and possibly physical as well as emotional fatigue.[17,18] Consequently, glutamine is considered a "conditionally indispensable amino acid" in hyper metabolic and hyper catabolic situations.[18] Schlemmer et al[19] reported that inflammation-related malnutrition is associated with glutamine depletion that in turn may contribute to fatigue in cancer patients. Cancer patients supported with glutamine had a lower NRS-2002 score and higher serum albumin levels after nutrition therapy compared to the control group in our study. However, this result did not affect the length of hospital stay or mortality. The role of supplementation with glutamine is still controversial despite some biologic rationale based on glutamine being semi essential in catabolic conditions. A recent narrative review on

the effects of glutamine supplementation on chemotherapy toxicity reported a clinical benefit in only 8 of 24 studies using oral glutamine and only 6 of 12 studies using parenteral glutamine.[18] Oral supplementation with glutamine (30 g/ day) for 4 weeks in patients with esophageal cancer enhanced lymphocyte mitogenic function and reduced permeability of the gut during radiochemotherapy.[20] Glutamine at a dose of 30 g/ day that was started one week before radiotherapy and continued for 2 weeks afterwards was reported to prevent weight loss and unplanned delays or interruptions of treatment and reduce the incidence and severity of radiation-induced esophagitis in 56 patients with locally advanced non-small cell lung cancer. [21]

There was no difference in NRS-2002 score after nutrition therapy between the HMB group and the control group in this study. In a randomized controlled trial (RCT), oral administration of a mixture of arginine, glutamine, and HMB for 24 weeks improved fat free mass compared to an isonitrogenous mixture of non-essential amino acids in advanced cancer patients.[4] A larger RCT in 472 cachectic cancer patients attempted to compare an oral mixture of HMB, glutamine, and arginine with an isonitrogenous control mixture but failed because of the difficulties in compliance with such a regimen over 8 weeks, with only 37% of the patients completing the protocol and no statistically significant differences being observed between the study groups.[5] While some results appear promising, data are inconsistent and these amino acid mixtures cannot be recommended for general use at this time in view of the reported compliance problems. ESPEN guidelines on nutrition in cancer patients recommend studying the effects of leucine and HMB in weight losing patients in large randomized trials.

Conclusion: We observed that patients who used standard enteral nutrition had higher NRS-2002 scores and lower serum albumin levels compared to patients receiving a combination of HMB, GLN and ARG or only GLN. We did not find any factor to be a good predictor of survival. There were difficulties with patient compliance during this study, as with many studies on patients with advanced cancer and there was a high percentage of missing or delayed data. Future randomly controlled studies on the effectiveness of using HMB or glutamine only in cancer patients is needed.

This retrospective study was carried out at Mersin University Hospital, Mersin, Turkey. The study was approved by the Ethics Committee of research of the Toros University (80706068.02-050/E4).

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Conflict of Interest: We have no conflict of interest to declare

Authorship: The work presented here was carried out in collaboration between all authors

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