World Nutrition Journal | eISSN 2580-7013

ORIGINAL PAPER

Protein and branched-chain amino acid intake are associated with functional capacity in malnourished head and neck cancer patients undergoing chemoradiotherapy

Received 27 February 2026
Accepted 12 May 2026
Published 31 August 2026

Link to DOI:
10.25220/WNJ.V10.i1.0003

Citation: Basalamah T, Manikam NRM, Tamin TZ, Lestari W, Sutanto K, Agung I. Protein and branched-chain amino acid intake are associated with functional capacity in malnourished head and neck cancer patients undergoing chemoradiotherapy. World Nutrition Journal.2026 August 31,10(i1): 19-29.

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Abstract

Introduction: Head and neck cancer (HNC) patients are at high risk of malnutrition and functional decline. Protein and branched-chain amino acids (BCAA) are key nutrients for muscle protein synthesis and may influence functional capacity. This study examined the association between protein and BCAA intake and functional capacity in malnourished HNC patients receiving chemoradiotherapy.

Methods: A cross-sectional study was conducted at a radiotherapy outpatient clinic among malnourished HNC patients undergoing chemoradiotherapy (week 4–5). Energy and protein intake were assessed using three non-consecutive 24-hour food recalls, while BCAA intake was estimated using a semi-quantitative FFQ. Functional capacity was evaluated using the six-minute walk test (6MWT). Associations were analyzed using Spearman's correlation test.

Results: A total of 94 participants were included (mean age 46.9 ± 11.9 years; 61.7% male), with most diagnosed at stage IV disease. Median protein intake was 40.65 g/day (0.79 g/kg BW/day), with 74.5% classified as having inadequate protein intake. Median total BCAA intake was 9.08 g/day. The mean 6MWT distance was 332.9 ± 123.9 m. Significant moderate positive correlations were found between protein intake and 6MWT distance ($r = 0.444$; $p < 0.001$) and between BCAA intake and 6MWT distance ($r = 0.419$; $p < 0.001$).

Conclusion: Protein and BCAA intake showed a moderate association with functional capacity among malnourished HNC patients undergoing chemoradiotherapy. These findings support the importance of optimizing protein and BCAA intake to preserve functional status during active cancer treatment.

Keywords: branched-chain amino acids, functional capacity, head and neck cancer, protein intake, six-minute walk test

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Introduction

Head and neck cancer (HNC) represents a group of malignancies that ranks seventh globally in terms of incidence, with an estimated 900,000 new cases occurring annually.[1] According to data from Cipto Mangunkusumo Hospital, nasopharyngeal carcinoma, as the most frequent type of HNC, ranks fourth among all cancer cases, with a total of 1,338 cases.[2] Patients with HNC are at high risk for malnutrition, the prevalence of severe malnutrition in this population reaches 53% based on the criteria established by the European Society for Clinical Nutrition and Metabolism (ESPEN).[3] Approximately 60% of HNC patients are diagnosed at an advanced stage, where chemotherapy and radiotherapy serve as the primary therapeutic modalities. Both modalities contribute significantly to the deterioration of nutritional status, with the prevalence of malnutrition and sarcopenia increasing two- to three-fold following treatment compared to baseline.[4,5]

Metabolic alterations in cancer trigger a state of hypercatabolism, including accelerated muscle protein catabolism, particularly of branched-chain amino acids (BCAAs), which play a pivotal role in the depletion of muscle mass. Branched-chain amino acids are essential for stimulating muscle protein synthesis through the activation of the mTOR (mammalian target of rapamycin) pathway.[6,7] Side effects of oncological therapy, such as chemotherapy and radiotherapy, further exacerbate malnutrition.[8] Approximately 50–90% of patients experience chemoradiation-induced side effects, including mucositis, dysphagia, nausea, and vomiting, which result in diminished dietary intake.[8] Research indicates that the majority of cancer patients maintain protein intakes below the recommended levels, specifically less than 1 g/kg BW/day.[9]

Inadequate protein intake can lead to a decline in muscle mass and strength, subsequently reducing physical mobility, quality of life scores, and functional capacity.[10] Assessing functional capacity in cancer patients is critical for determining prognosis and treatment response, utilizing subjective methods such as the Karnofsky Scale as well as objective measures like the 6-minute walk test (6MWT) and the handgrip strength test.[11,12] Compared with other methods, the 6MWT provides a more comprehensive assessment of functional capacity by reflecting overall physical condition, including muscle strength, motor function, and cardiorespiratory fitness. As a submaximal exercise test, it is safe and well tolerated by patients with cancer.[11] Beyond being practical and cost-effective, this test serves as a prognostic indicator, a walking distance of ≥ 400 meters is associated with improved life expectancy.[11,12] Cancer patients with increased muscle strength and reduced fatigue tend to demonstrate better performance and greater distances in the 6MWT.[13] In HNC patients undergoing chemotherapy, a reduction in 6MWT distance has been observed starting from the end of the third week of therapy.[14]

The combination of adequate protein intake and sufficient physical activity facilitates muscle synthesis, thereby enhancing functional capacity.[14] A study on lung cancer patients found that protein intake correlates positively with improved functional capacity as measured by the Karnofsky Scale.[15] In advanced-stage cancer patients with malnutrition undergoing chemotherapy, whey protein supplementation at 1.5 g/kg BW/day for three months has been shown to improve handgrip strength as measured by digital hand dynamometry.[16]

The majority of previous studies regarding the role of protein and BCAAs in functional capacity have focused on supplementation-based interventions. This study, however, does not focus on supplementation; rather, it evaluates actual intake derived from daily dietary patterns. This approach potentially offers better adherence as it is more affordable and accessible for patients. In addition, this study employs the 6MWT as a more objective measure of functional capacity, reflecting overall muscle function more comprehensively than commonly used methods such as the subjective Karnofsky score or the handgrip strength test that assesses only specific muscle groups. Therefore, this study is important to further clarify the relationship between protein and BCAA intake and the functional capacity of malnourished HNC patients undergoing chemoradiotherapy.

Methods

Study design and population

This cross-sectional study was conducted at the Radiotherapy Outpatient Clinic of Dr. Cipto Mangunkusumo National General Hospital, Jakarta, from August to November 2025. The samples of this study were 94 participats who met the inclusion and exclusion criteria and were recruited using consecutive sampling. Patients with HNC undergoing radiotherapy were identified from the daily clinic list. Eligible patients were approached during their clinic visits and invited to participate, and those who agreed provided written informed consent prior to enrollment.

Eligible participants were male and female patients aged 19–59 years who were diagnosed with HNC, had received chemotherapy, were undergoing radiotherapy in weeks 4–5, and were classified as malnourished based on The American Society for Parenteral and Enteral Nutrition (ASPEN) criteria. Exclusion criteria included inability to ambulate independently, high risk of falls, history of unstable angina or myocardial infarction within the past month, and chronic liver disease. This study has obtained research permit from Research Ethics Committee at the Faculty of Medicine, Universitas Indonesia with a research protocol KET-1083/UN2.F1/ETIK/PPM.00.02/2025.

Anthropometric measurements included body weight and height, measured twice and averaged. Nutritional status was determined using the ASPEN malnutrition criteria. Dietary data were collected by trained dietitians experienced in nutritional assessment, following standardized procedures to ensure consistency. Energy and protein intake were assessed using a 3×24-hour food recall conducted on nonconsecutive days. Protein intake reflected total consumption from both habitual dietary sources and any oral nutritional supplements consumed by the participants. Intake of BCAA was assessed using a semi-quantitative food frequency questionnaire adapted from a previously published study.[17,18] Participants were asked to report their usual dietary intake over the past month. To enhance the accuracy and consistency of dietary data collection, standardized portion size estimation tools (e.g., household measures and food models) were used, and probing techniques were applied by trained dietitians during interviews to minimize recall bias and reduce underreporting. All data were analyzed using Nutrisurvey 2007.

Physical activity was evaluated using the International Physical Activity Questionnaire–Short Form. Functional capacity was assessed using the 6-MWT following American Thoracic Society guidelines. Participants were instructed to walk as fast as possible, without running, back and forth along a flat, straight 30-m track for six minutes, and the total cumulative distance covered (meters) was recorded as the measure of functional capacity.

Statistical Analysis

Statistical analysis was performed using SPSS version 20. Data distribution was assessed using the Kolmogorov–Smirnov test. Normally distributed variables are presented as mean and standard deviation, while non-normally distributed variables are presented as median (minimum–maximum). Correlations between protein intake, BCAA intake, and functional capacity were analyzed using Pearson or Spearman correlation tests as appropriate.

Results

Among the 102 participants who consented to data collection, 8 were excluded (not meeting ASPEN malnutrition criteria, n = 4; inability to ambulate independently, n = 3; liver disease, n = 1), leaving 94 participants for analysis.

Table 1. Characteristics of patients

Characteristics	Results (n = 94)	Moderate malnutrition (n=37)	Severe malnutrition (n=57)	*p*-value
Age (years)	46.9 ±11.9	48.5 ±11.5	45.9 ±12.2	0.878
Sex, n (%)				
Men	58 (61.7)	22 (37.9)	36 (62.1)	0.719
Female	36 (38.3)	15 (41.7)	21(58.3)	
Cancer site, n (%)				
Nasopharynx	42 (44.7)	15 (35.7)	27 (64.3)	0.834
Sinonasal	14 (14.9)	6 (42.9)	8 (57.1)	
Tongue	12 (12.8)	5 (41.7)	7 (58.3)	
Larynx	16 (17)	8 (50)	8 (50)	
Others	10 (10.6)	3 (30)	7 (70)	
Cancer stage (n, %)				
II	2 (2.1)	1 (50)	1 (50)	0.025
III	22 (23.4)	14 (63.6)	8 (36.4)	
IV	70 (74.5)	22 (31.4)	48 (68.6)	
Radiation fraction	18.7 ±2.6	18.4 ±2.4	19 ±2.6	0.241
Body mass index (kg/m^2)	20.2 ±4.3	22.9 ±4.2	18.4 ±3.4	<0.001
Physical activity level (n,%)				
Low	79 (84)	32 (40.5)	47 (59.5)	0.789
Moderate	15 (16)	5 (33.3)	10 (66.7)	
High	0			
Energy intake (kcal/day)	1060 (308-2461)	1102 (308-2461)	1052 (496-2300)	0.425
Energy intake (kcal/kg BW/day)	21 (4-50)	20 (4-50)	22 (9-40)	0.276
Energy adequacy, (n,%)				
Low	75 (79.8)	32 (42.7)	43 (57.3)	0.193
Adequate	19 (20.2)	5 (26.3)	14 (73.7)	

Data are presented as mean ± SD, median (min–max), or n (%). Continuous variables were compared using independent samples t-test or Mann–Whitney U test according to distribution. Categorical variables were compared using chi-square or Fisher's exact test, as appropriate.

The mean age was 46.9 ± 11.9 years, and most participants were male (61.7%). The nasopharynx was the most common tumor site (44.7%), and most participants had stage IV disease (74.5%). Based on ASPEN malnutrition criteria, participants were categorized into moderate malnutrition (39.4%) and severe malnutrition (60.6%) groups. The mean body mass index was 20.2 ± 4.3 kg/m². Most participants had low physical activity (84.0%), and the median energy intake was 21.0 kcal/kg BW/day, with 79.8% showing low energy adequacy (<30 kcal/kg BW/day). Baseline characteristics were generally comparable between the moderate and severe malnutrition groups. However, participants with severe malnutrition had a significantly lower BMI than those with moderate malnutrition (18.5 ± 3.4 vs. 22.9 ± 4.3 kg/m², $p < 0.001$). Cancer stage distribution also differed significantly between groups ($p = 0.025$), with stage IV disease being more frequent in the severe malnutrition group. Participant characteristics are presented in **Table 1**.

Protein and BCAA Intake

The median protein intake was 40.65 g/day (range: 5.0–128.8 g/day), equivalent to 0.79 g/kg BW/day (range: 0.10–2.47 g/kg BW/day); 74.5% of participants did not meet the recommended intake of ≥1.2 g/kg BW/day. The median total BCAA intake was 9.08 g/day (range: 1.21–33.92 g/day), with median intakes of leucine, isoleucine, and valine of 4.20 g/day (0.80–15.13 g/day), 2.22 g/day (0.22–9.46 g/day), and 2.42 g/day (0.19–9.33 g/day), respectively (**Table 2**).

Table 2. Protein intake among study subjects

Characteristics	Results (n = 94)
Protein intake (g/day)	40.65 (5.0–128.8)
Protein intake (g/kg BW/day)	0.79 (0.10–2.47)
Protein adequacy (n, %)	
Low	70 (74.5)
Adequate	24 (25.5)
Total BCAA intake (g/day)	9.08 (1.21 – 33.92)
Leucine intake (g/day)	4.20 (0.80 – 15.13)
Isoleucine intake (g/day)	2.26 (0.22 – 9.46)
Valine intake (g/day)	2.42 (0.19 – 9.33)

Functional Capacity (6-Minute Walk Test)

The mean 6MWT distance was 332.9 ± 123.9 m. Male participants achieved significantly longer walking distances than female participants (354.7 ± 115.1 m vs 297.8 ± 131.0 m, $p = 0.030$) (**Table 3**).

Table 3. Six-minute walk test results among study subjects

Characteristics	Results (n = 94)	p value
6MWT (m)	332.9 ±123.9	
6MWT by sex (n, %)		
Men	354.7 ±115.1	0.030[a]
Female	297.8 ±131.0	

[a] Independent samples t-test.

Association between Protein Intake, BCAA Intake, and Functional Capacity

Protein intake was positively correlated with 6MWT distance (r = 0.444; p < 0.001). A similar positive association was observed between BCAA intake and functional capacity (r = 0.419; p < 0.001), indicating that higher protein and BCAA intakes were associated with better functional capacity, as shown in **Table 4**.

Tabel 4. Association of protein and BCAA intake with functional capacity among study subjects

Variable	6MWT	
	r value	p value
Protein intake	0.444[†]	<0.001[a]
BCAA intake	0.419[†]	<0.001[a]

Notes: BCAA, branched-chain amino acids; r, correlation coefficient; p, level of significance. [a] Spearman correlation test.

To account for potential confounding factors, multivariable linear regression analysis was performed adjusting for sex, body mass index, cancer stage and physical activity level. Protein and BCAA intake were analyzed in separate models.

Protein intake remained independently associated with 6MWT distance (B = 95.58, 95% CI: 46.41–144.75, p < 0.001). Similarly, BCAA intake was independently associated with functional capacity (B = 7.54, 95% CI: 3.22–11.86, p = 0.001).

Physical activity level was also significantly associated with 6MWT distance in both models (p = 0.019), while sex showed a borderline association. Cancer stage was not significantly associated with functional capacity.

Tabel 5. Multivariable linear regression analysis of protein and BCAA intake in relation to functional capacity

Variable	**Protein Model B (95% CI)**	**p-value**	**BCAA Model B (95% CI)**	**p-value**
Protein intake	95.58 (46.41–144.75)	<0.001	—	—
BCAA intake	—	—	7.54 (3.22–11.86)	0.001
Sex	-43.72 (-89.96–2.53)	0.064	-46.46 (-93.27–0.35)	0.052
Body mass index	-0.47 (-5.94–4.99)	0.864	-2.97 (-8.43–2.48)	0.281
Cancer stage	-21.66 (-68.67–25.36)	0.362	-24.28 (-72.02–23.46)	0.315
Physical activity	74.70 (12.58–136.81)	0.019	75.86 (12.77–138.94)	0.019

Notes: B, unstandardized regression coefficient; CI, confidence interval. Multivariable linear regression models were adjusted for sex, body mass index, physical activity level, and cancer stage. Cancer stage was categorized into stage II–III and stage IV. Protein and BCAA intake were analyzed in separate models to avoid collinearity.

Discussion

This study evaluated the association between protein and BCAA intake with functional capacity among malnourished patients with HNC undergoing concurrent chemoradiotherapy All participants were receiving active treatment and were characterized by advanced cancer stage, low physical activity levels, and poor nutritional status according to ASPEN criteria.

Protein and BCAA intakes in this study were generally inadequate, with most participants failing to achieve recommended intake levels. Although the relative contributions of leucine, isoleucine, and valine followed expected dietary patterns, absolute BCAA intake remained low. Similar findings have been reported among patients with HNC undergoing radiotherapy or chemoradiotherapy, indicating substantial nutritional challenges during active treatment. By comparison, Kristian et al.,[18] observed higher protein and BCAA intakes in patients who had not yet initiated active therapy, highlighting the adverse impact of treatment-related side effects on dietary intake. In addition to medical factors, social determinants such as education level, economic status, food access, and family support may further contribute to inadequate protein and BCAA intake during intensive cancer treatment.[19]

Functional capacity, assessed using the 6-MWT, was markedly reduced in this study compared with reference values in healthy individuals. This reduction aligns with findings reported by Mukhlisah et al.,[20] who demonstrated a significant decline in 6-MWT distance following chemotherapy. The impaired functional capacity observed in this population reflects the combined effects of systemic inflammation, cancer-related fatigue, reduced physical activity, and progressive loss of muscle mass during chemoradiotherapy.

Cancer-related metabolic changes induce a hypercatabolic state characterized by increased muscle protein breakdown, particularly of BCAA, leading to loss of muscle mass.[6,7] In patients undergoing chemoradiotherapy, treatment-related side effects such as mucositis, dysphagia, nausea, and vomiting frequently reduce dietary intake, resulting in suboptimal protein consumption.[8] Consequently, suboptimal protein intake may attenuate its impact on functional performance, as reflected in measures such as the 6-MWT.[10,14]

A significant positive correlation was observed between protein intake and functional capacity in this study, supporting evidence that higher protein intake is associated with better physical performance in patients with cancer. Umaya et al.,[15] reported a positive association between dietary protein intake and functional status measured by the Karnofsky Performance Scale, while Ford et al.,[21] demonstrated improvements in physical performance among patients with colorectal cancer receiving higher protein intake during chemotherapy. These findings suggest that adequate protein intake may contribute to the preservation of functional capacity, even in the absence of measurable gains in muscle mass.

However, not all studies have demonstrated a functional benefit of higher protein intake. Uster et al.,[22] reported no improvement in functional capacity among patients with advanced gastrointestinal and lung cancer despite combined nutritional counseling targeting adequate protein intake and structured exercise. This lack of effect was attributed to refractory cachexia, advanced disease stage, older age, and reduced anabolic responsiveness. These findings indicate that the relationship between protein intake and functional capacity is likely context-dependent and may be attenuated in patients with severe metabolic impairment or those in late or palliative stages of disease.

In this study, BCAA intake was positively associated with functional capacity. Biologically, BCAAs, particularly leucine, stimulate muscle protein synthesis through activation of the mTOR signaling pathway and may attenuate muscle protein breakdown during catabolic stress.[23,24] Consistent with these mechanisms, studies in non-cancer populations by Park et al.,[25] and Liao et al.,[26] demonstrated positive associations between dietary BCAA intake and muscle strength, walking speed, and overall physical function. In oncology settings, Storck et al. similarly reported improvements in muscle strength among patients with advanced cancer receiving leucine-enriched amino acid supplementation combined with exercise, supporting the functional relevance of BCAA under catabolic conditions.

By comparison, Kusumawati et al.,[27] and Fauzarianda et al.,[28] reported no significant association between BCAA intake and functional outcomes in cancer patients, particularly among those with more stable nutritional status and not receiving radiotherapy. These findings indicate that the functional benefits of BCAA intake may be more evident under conditions of active treatment and malnutrition, as observed in the present study.

Multivariable analysis further confirmed the independent association between nutritional intake and functional capacity. After adjusting for sex, body mass index, physical activity level, and cancer stage, both protein and BCAA intake remained significantly associated with 6MWT distance. These findings suggest that the relationship between protein and BCAA intake and functional capacity is not solely explained by differences in baseline characteristics or disease severity.

Physical activity level also remained significantly associated with functional capacity, highlighting its important role alongside nutritional intake. In contrast, cancer stage was not significantly associated with 6MWT distance in the adjusted models, suggesting that nutritional factors may play a role in maintaining functional capacity regardless of disease stage.

Taken together, the findings of this study emphasize the importance of adequate protein and BCAA intake in maintaining functional capacity among malnourished patients with HNC undergoing chemoradiotherapy. Differences in findings across studies may be influenced by disease stage, treatment phase, age, and baseline nutritional status. These results support the integration of targeted nutritional strategies alongside physical activity interventions to mitigate functional decline during active cancer treatment.

This study has several strengths, including relatively homogeneous clinical characteristics and the use of an objective measure of functional capacity. However, the cross-sectional design limits causal inference, and dietary assessment is subject to recall bias. In addition, BCAA intake estimation relied on the USDA food composition database due to the lack of local data, which may limit the precision of BCAA intake assessment for Indonesian foods.

Conclusions

This study demonstrates that inadequate protein and BCAA intake is common among malnourished patients with HNC undergoing concurrent chemoradiotherapy and is associated with reduced functional capacity. Protein and BCAA intake were positively associated with better functional performance, suggesting a potential role in mitigating functional decline during active treatment. The findings highlight the importance of early and targeted nutritional strategies, particularly those emphasizing adequate protein and

BCAA intake, to support functional capacity in this vulnerable population. Future longitudinal and interventional studies are needed to clarify causal relationships and to determine optimal nutritional approaches across different stages of treatment and disease severity.

Conflict of interest

The authors declared no conflict of interest regarding this article.

Ethic Statement

Written informed consent was obtained from the participant prior to data collection.

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Author Contributions

TB: Conceptualization, data acquisition, formal analysis, interpretation of results, drafting of the manuscript, and final approval of the version to be published;
NRMM: Conceptualization, supervision, critical revision of the manuscript, interpretation of data, and final approval of the version to be published;
TZ. Tamin: Supervision, critical revision of the manuscript, interpretation of data, and final approval of the version to be published;
WL, KS, and IA: Supervision, critical revision of the manuscript for important intellectual content, and final approval of the version to be published.

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