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Research Article

Plasma Copper Level Correlates With Body Mass Index–Adjusted Body Weight Loss Grades and Total Fat Mass in Male Patients With Recurrent or Metastatic Head and Neck and Nasopharyngeal Cancers

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Purpose: There is a lack of comprehensive analysis on the associations between malnutrition, body composition, and clinical, anthropometric, biochemical, nutrition-inflammation markers, mineral and trace element levels, cytokine concentrations, and antioxidant activity in patients with cancer. Differences regarding sex at birth, ethnicity, and cancer types and stages further contribute to variations in body composition and mineral and trace element levels. This study examines factors associated with malnutrition and body composition, adjusting for relevant clinical, biochemical, nutritional data, and lifestyle confounders.
Methods: In total, 78 male patients with recurrent or metastatic head and neck cancer (HNC) or nasopharyngeal carcinoma (NPC) were recruited. Clinical characteristics (e.g., age, tumor status, and performance status), lifestyle factors, anthropometric data, nutrition-inflammation markers, plasma levels of minerals, trace elements, and cytokines as well as antioxidant activity were determined and analyzed using multivariable logistic regression and analysis of covariance models.
Results: Half of the patients (50.3%) exhibited advanced grades of BMI-adjusted body weight loss (BWL), and nearly 90% had C-reactive protein levels exceeding 5 mg/L, reflecting poor nutritional status and elevated inflammation, despite being medically fit for chemotherapy. Plasma copper levels were independently associated with BMI-adjusted BWL as well as with lean body mass and total fat mass. Similarly, plasma zinc levels showed an independent association with total fat mass.
Conclusions: Plasma levels of trace elements, including copper and zinc, are strongly correlated with malnutrition and body composition in male patients with recurrent or metastatic HNC or NPC.

Keywords: body composition; copper; head and neck cancer; malnutrition; nasopharyngeal cancer; trace elements

1. Introduction

Malnutrition is highly prevalent at the time of diagnosis in both patients with head and neck cancer (HNC) and nasopharyngeal cancer (NPC) [1, 2]. This condition not only delays treatment progression and increases drug toxicity but also contributes to a poor quality of life, elevated healthcare costs, and unexpected mortality [3–7]. Malnutrition may be accompanied by diverse clinical symptoms, such as anorexia, dysphagia, and frailty, and it is often characterized by significant body weight loss (BWL) or a reduced body mass index (BMI). These changes frequently reflect alterations in lean body mass (LBM) and total fat mass (TFM), which are critical components of body composition [4, 8, 9]. Importantly, pretreatment LBM and TFM have been strongly associated with treatment toxicity, early treatment failure, recurrence-free survival, and overall survival in these patients [10–14].

Malnutrition is frequently observed in patients with cancer due to factors such as aging, lifestyle, comorbidities, and tumor characteristics. These factors reflect both the patient's inherent traits and cancer-related influences, resulting in nutritional and inflammatory changes. Systemic inflammation is a key contributor to the pathogenesis of cancer-associated malnutrition. During the inflammatory response, mediators such as cytokines and reactive oxygen species (ROS) drive the progression of malnutrition (1, 3). Circulating pro-inflammatory cytokines—including tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), interleukin-6 (IL-6), and interferon-gamma (IFN-γ)—act synergistically to disrupt carbohydrate, protein, and lipid metabolism. These disruptions promote muscle proteolysis and stimulate lipolysis, ultimately leading to BWL and the development of cachexia. Additionally, these cytokines affect the central nervous system, impairing appetite regulation and contributing to anorexia and reduced nutritional intake [1, 2, 15]. Various methods are used to estimate the severity of malnutrition in patients with HNC and NPC [1], including a variety of clinical assessments, such as anthropometric measurements (BWL, BMI, and arm/waist circumference), nutrition risk index determination, patient-generated subjective global assessment, body composition evaluated using dual-energy X-ray absorptiometry (DXA) and computerized tomography, and biological marker determination, including albumin, C-reactive protein (CRP), and circulating cytokines [1]. A recently developed clinical grading system that combines BMI and the severity of BWL (BMI-adjusted BWL) offers a practical and reliable approach for assessing malnutrition and predicting survival in patients with HNC and NPC. This system is independent of traditional prognostic factors, such as tumor stage and performance status [15].

Malnutrition-induced changes in body composition and inflammation disrupt the homeostasis of minerals and trace elements, which, though present in small amounts, play vital roles in the metabolism of proteins, lipids, carbohydrates, and nucleic acids [16]. Similarly, imbalances in these minerals and trace elements can induce considerable disturbances in macronutrient metabolisms, potentially accelerating the progression of cancer and worsening malnutrition.

Key minerals, such as calcium, phosphorus, magnesium, sodium, and potassium, are integral to various anatomical structures, including bones, nucleic acids, muscles, and fat tissue. For example, a meta-analysis reported that calcium helps reduce fat deposition [17]. Additionally, a rapid decrease in magnesium levels can trigger inflammation by disrupting its balance with calcium antagonists. This imbalance causes an increase in intracellular calcium, activating phagocytic cells that release inflammatory cytokines. These cytokines, in turn, promote oxidative stress, contributing to the deposition and accumulation of fatty tissue [18]. Essentially, a deficiency in trace elements may be associated with an increase in fat deposition [19].

Approximately 23.3% of the total copper in the body of an adult is stored in the muscles [20]. Copper levels are inversely related to muscle and bone weight. Copper is essential for synthesizing superoxide dismutase (SOD), and its deficiency can increase muscle damage due to oxidative stress. Copper also regulates body lipids, as its deficiency inhibits semicarbazide-sensitive amine oxidase activity—a critical enzyme in adipocyte energy metabolism—leading to adipocyte hypertrophy and fat deposition [21].

Approximately 60% and 30% of the total body content of zinc can be found in muscles and bones, respectively [22]. Zinc levels are associated with BMI, waist circumference, and waist-to-hip ratio [23]. Plasma zinc concentrations inversely correlate with abdominal skinfold thickness; therefore, low levels are linked to increased abdominal fat [24]. Zinc deficiency elevates circulating cytokines and ROS, inducing oxidative stress and promoting obesity [25]. Furthermore, zinc and magnesium deficiencies have been implicated in oxidative stress, sarcopenia, and excessive fat mass accumulations [26, 27].

Selenium functions as a cofactor for antioxidant enzymes, such as glutathione peroxidase (GPx) and SOD, which reduce the oxidative stress induced by ROS [28]. Selenium may protect muscles from inflammation and oxidative stress [22]. Studies indicate that selenium regulates lipid metabolism and inhibits fat formation by modulating selenoproteins and oxidative stress–related gene expression [29, 30]. A cross-sectional study reported a negative association between selenium levels and both systemic and central obesity [31]. Notably, these minerals play a synergistic role in the regulation of body composition [32].

Nonetheless, data on the association between minerals and body composition show significant variability due to multiple factors, such as sex assigned at birth, target population, illnesses, and ethnicity [23]. For example, individuals assigned to different sexes show distinct plasma levels of calcium, phosphorus, zinc, and copper [22]. Bertinato et al. demonstrated that low serum magnesium concentrations were linked to excess body mass, insulin resistance, and diabetes in women but not in men [33]. Similarly, significantly higher plasma copper and phosphorus concentrations were observed in females compared to males [34]. In a study involving 1896 participants from the Korean National Health and Nutrition Examination Survey,

zinc was directly associated with body fat distribution and abdominal obesity in men but not in women [35]. These findings highlight the need for a comprehensive analysis using a uniform study population to accurately assess the role of minerals and trace elements in body composition.

Altered levels of minerals and trace elements have also been observed in patients with HNC and NPC compared to healthy controls [36–39]. In this study, we minimized confounding factors related to sex assigned at birth, population heterogeneity, and disease variability by enrolling a uniform group of male patients with HNC and NPC. These patients were planning to undergo palliative chemotherapy for either newly diagnosed metastatic disease or first recurrence. Our goal was to investigate factors influencing malnutrition—assessed through BMI-adjusted BWL grades—and body composition—evaluated using DXA. To account for potential confounding variables, we adjusted for age, tumor status, medical performance, and lifestyle factors (e.g., smoking, alcohol consumption, and betel nut use). The study also includes data from hemograms, clinical biochemistry, anthropometry, nutrition indices, inflammatory markers, and plasma mineral, trace element, cytokine, and oxidative stress levels from all patients.

2. Materials and Methods

2.1. Patient Recruitment. We conducted a cross-sectional enrollment of eligible male patients diagnosed with histologically confirmed squamous cell carcinoma of the head and neck, encompassing cancers of the oral cavity, oropharynx, nasopharynx, hypopharynx, and larynx, between June 2017 and December 2022. Patients met one of two inclusion criteria: (1) they had previously undergone definitive surgery, chemotherapy, or radiotherapy and were disease-free for over 6 months, but experienced their first recurrence within one month prior to the study, or (2) they were newly diagnosed with metastatic cancer and had not received any prior anticancer treatment. Recurrence or metastatic statuses were confirmed by the Head and Neck Cancer Committee based on the 8th edition of the American Joint Committee on Cancer (AJCC) staging system.

Inclusion criteria also encompassed an Eastern Cooperative Oncology Group (ECOG) performance status of 2 or lower, age under 75, adequate hematopoietic and organ function, and p16-negative expression in head and neck or nasopharyngeal tumors. Exclusion criteria comprised systemic illnesses such as New York Heart Association Class IV heart failure, severe chronic obstructive pulmonary disease (COPD), major gastrointestinal disorders, decompensated liver cirrhosis, end-stage renal disease, uncontrolled diabetes, chronic infections, autoimmune diseases, or regular use of vitamin or trace element supplements.

Informed written consent was obtained from all patients with cancer and control participants at the time of enrollment. The study received approval from the Institutional Review Board of Chang Gung Memorial Hospital, Taiwan (approval number: 201601395A3C506) and was conducted in compliance with the Good Clinical Practice Guidelines and the Declaration of Helsinki.

2.2. Clinicopathological Data. Clinicopathological data were collected from all participants, including age, body weight (BW), height, ECOG performance status, comorbidities (e.g., hypertension, diabetes mellitus, dyslipidemia, and COPD), tumor site, tumor stage, tumor size (T), regional lymph node involvement (N), and their histories on cigarette smoking, alcohol consumption, and betel nut use were recorded. Patients who were current smokers or had a history of smoking were classified as smokers. Those consuming alcohol more than four times per week were categorized as alcohol drinkers. Individuals who had used betel nuts within the past year were identified as betel nut users. BMI was calculated as weight (kg) divided by height (m^2), that is, kg/m^2. The percentage of BWL was determined using the following formula: ((current weight in kg − previous weight in kg)/previous weight in kg) × 100, where previous weight referred to BW measured six months prior to diagnosis.

The grading system combining BMI and %BWL for nutrition assessment was used as previously described [15]. In brief, five grades were defined based on the combination of both BMI and %BWL, as follows [15]:

- Grade 0: %BWL < 2.5 and BMI > 25.
- Grade 1: %BWL < 2.5 and BMI 20–25 kg/m^2 or %BWL 2.5–6 and BMI ≥ 28.
- Grade 2: %BWL 2.5–6 and BMI 20–28 or %BWL 6–11 and BMI ≥ 28.
- Grade 3: %BWL < 2.5 and BMI < 20 or %BWL 2.5–6 and BMI < 20, or %BWL 6–11 and BMI 20–28, or % BWL 11–15 and BMI > 22, or %BWL ≥ 15 and BMI ≥ 28.
- Grade 4: %BWL 6–11 and BMI < 20, or %BWL 11–15 and BMI < 22, or %BWL ≥ 15 and BMI < 28.

2.3. Evaluation of LBM and TFM. We utilized dual-energy fan-beam X-ray absorptiometry (Lunar iDXA, GE Medical Systems, Madison, WI, USA) to measure total body composition. The scanner software automatically selected the appropriate scan mode (standard, thin, or thick) based on each participant's BMI and body size. Scans were processed using enCORE software, v15 (GE Lunar), following the International Society for Clinical Densitometry's guidelines to ensure proper participant positioning and accurate measurements [40]. LBM and TFM were measured and analyzed within 1 week after enrollment.

2.4. Hemograms, Biochemical Data, and Nutrition-Inflammation Markers (NIMs). Blood samples were collected after overnight fasting within 1 week of enrollment. Hemograms, biochemical data, and NIMs were analyzed, including hemoglobin (Hb, g/dL), white blood cell count (WBC, $10^3/mm^3$), platelet count ($10^3/mm^3$), albumin (g/dL), creatinine (mg/dL), alanine transaminase (ALT, U/L), total bilirubin (mg/dL), uric acid (mg/dL), fasting glucose (mg/dL), total cholesterol (mg/dL), triglycerides (mg/dL), and CRP (mg/dL). Measurements were performed using an

auto-analyzer (Beckman, USA) at the central laboratory of CGMH in Keelung, Taiwan.

The estimated glomerular filtration rate (eGFR, mL/min/1.73 m^2) was calculated using the abbreviated Modification of Diet in Renal Disease Study equation, adjusted for a body surface area of 1.73 m^2. Total lymphocyte count (TLC) was derived by multiplying the WBC count ($10^3/mm^3$) by the percentage of lymphocytes in the blood.

2.5. Plasma Cytokine Level Determination. Plasma cytokines, including TNF-α, IFN-γ, IL-1β, IL-6, IL-8, and vascular endothelial growth factor (VEGF), were collected from patients before treatment. Samples were stored at −80°C in pyrogen-free plastic tubes until analysis. Cytokine levels were measured using enzyme-linked immunosorbent assay (ELISA) and quantified by the MILLIPLEX human cytokine/chemokine/growth factor—immunology multiplex assay (HCYTA-60K, Merck, Darmstadt, Germany) following the manufacturer's protocol. Final concentrations were determined using an xMAP INTELLIFLEX counter (Merck). All blood samples were thawed only once and analyzed in triplicate to ensure accuracy.

2.6. Plasma Mineral Level Determination. The levels of calcium (mg/dL), phosphorus (mg/dL), magnesium (mEq/L), sodium (mEq/L), potassium (mEq/L), and chloride (mEq/L) were measured using an auto-analyzer (Beckman, USA) at the central laboratory of CGMH in Keelung, Taiwan.

The concentrations of plasma selenium, copper, and zinc were measured using a flame atomic absorption spectrophotometer (932 Plus, GBC, Australia) equipped with an air-acetylene flame, at wavelengths of 196.0, 324.71, and 213.9 nm, respectively, without any background correction. Absorbance for each sample was measured in triplicate in a peak-height mode. Samples were digested with a H_2O_2/HNO_3 mixture using a Start D microwave-assisted digestion system (Milestone Microwave Labstation ETHOS D) and subsequently diluted to volume with double-deionized water. The accuracy of the method was confirmed through comparison with certified serum reference materials (Level 2, NO0371, Seronorm, Nycomed, Oslo, Norway) [41]. Fasting blood samples were collected within one week of enrollment and stored at −80°C in pyrogen-free tubes until analysis.

2.7. Antioxidant Enzyme Activity in Plasma. The activities of three plasma enzymes—GPx, SOD, and catalase—were measured as indicators of antioxidative capacity [41]. GPx activity was assessed using GPx assay kits (Cayman Chemical, catalog #703102, Ann Arbor, Michigan, USA). In this assay, oxidized glutathione, generated by reducing ROS, is recycled to its reduced form by NADPH and glutathione reductase. The rate of NADPH consumption reflected the formation rate of oxidized glutathione, and GPx activity was expressed as nmol NADPH oxidized/min/mL.

SOD activity was measured using SOD assay kits (Cayman Chemical, catalog #706002). One unit of SOD activity was defined as the enzyme amount required to achieve 50% dismutation of superoxide radicals, and activity was reported as U/mL. Catalase activity was determined using catalase assay kits (Cayman Chemical, catalog #707002). In this assay, catalase catalyzes the reaction of methanol and hydrogen peroxide to produce formaldehyde. Catalase activity was expressed as nmol formaldehyde produced/min/mL [41]. Within one week of enrollment, fasting blood samples were obtained and preserved at −80°C in pyrogen-free plastic tubes for subsequent analysis.

2.8. Plasma Oxidative Stress Level Determination. Thiobarbituric acid (TBA) reactive substances (TBARS) were measured as markers of lipid peroxidation, providing an indicator of oxidative stress. Plasma TBARS levels were assessed using a TBARS assay kit (Cayman Chemical, catalog #10009055). The assay involved the detection of the malondialdehyde (MDA)-TBA adduct, which forms when MDA reacts with TBA under acidic conditions and elevated temperatures. The resulting adduct was quantified colorimetrically at 530–540 nm; TBARS concentrations was reported in μM. Within one week of enrollment, fasting blood samples were collected and stored at −80°C in pyrogen-free plastic tubes pending analysis.

2.9. Statistical Analysis. Statistical analyses were conducted using SPSS v22.0 (SPSS Inc., Chicago, IL, USA). Before analysis, the normality of all continuous variables was assessed using the Kolmogorov–Smirnov test. Univariate associations between clinical variables, biochemical measurements, electrolyte levels, anthropometric data, NIMs, cytokine concentrations, oxidative stress, and antioxidant enzyme activities with BMI-adjusted BWL grades were first evaluated using Chi-square tests for categorical variables, and independent *t*-tests or nonparametric Mann–Whitney tests for continuous variables, depending on the normality of the data. Variables significantly associated with BMI-adjusted BWL grades ($p < 0.05$) in the univariate analysis were subsequently included in a multivariate logistic regression analysis.

Univariate associations between clinical variables, biochemical measurements, electrolyte levels, anthropometric data, NIMs, cytokine concentrations, oxidative stress, and antioxidant enzyme activities with LBM and TFM were assessed using Pearson or Spearman correlation coefficients, independent *t*-tests, nonparametric Mann–Whitney tests, or analysis of variance (ANOVA), based on the normality of the data. Variables significantly associated with LBM or TFM ($p < 0.05$) in the univariate analysis were then included in a multivariate non-parametric analysis of covariance (ANCOVA).

Nonparametric ANCOVA was performed to examine the effect of variables significantly associated with LBM or TFM from the univariate analysis. Given the non-normality of LBM and TFM, the aligned ranks transformation method was applied, which adjusts for differences in distributions and ranks the data, making them suitable for analysis. The aligned ranks transformation was applied to LBM and TFM and followed by a standard ANCOVA, with a statistical

power of 0.8, an alpha level of 0.05, and a medium-to-large effect size ($f = 0.30$). Based on these parameters, a minimum of 75 participants was estimated to be required to achieve sufficient power.

3. Results

A total of 78 male patients with HNC/NPC were included in the study. Table 1 provides a summary of the clinical characteristics, anthropometric measurements, DXA-derived LBM and TFM, biochemical data, electrolyte levels, NIMs, plasma cytokine levels, plasma mineral and trace element concentrations, and plasma antioxidant activity for the entire cohort. On average, the patients were 56.3 years old, with a median age of 58 years. Nearly 90% of the patients had an ECOG performance status ≤ 1. The most common tumor site was the oral cavity (56.4%), followed by the oropharynx (14.1%) and NPC (14.1%). Most patients presented with advanced tumor stages (T3 + T4, 67.9%), regional lymph node involvement (N2–N3, 60.3%), and first recurrences (M0, 75.6%). Over half of them had a history of smoking, alcohol use, and betel nut chewing. Approximately 20% of the patients had hypertension or dyslipidemia, while 10% had diabetes or COPD.

The hemogram, TLC, albumin, renal and hepatic function, and electrolyte, uric acid, fasting glucose, total cholesterol, and triglyceride levels of the patients were generally within normal ranges, with the exception of chloride levels, which were reduced. In addition, CRP levels were significantly elevated, averaging 25.57 mg/L, whereas 59 patients (75.6%) had CRP levels exceeding 5 mg/L. Selenium and copper levels were within normal ranges, while the zinc level, at 56.83 μg/dL, was below the normal range.

In terms of malnutrition assessment, the average BWL was −7.96%, with nearly 90% of the patients experiencing a BWL greater than 5%, one-third having a BMI below 18.5 kg/m^2, and half presenting advanced grades (3 + 4) of BMI-adjusted BWL. Although the average albumin level was 3.8 g/dL, 20% of the patients had less than 3.5 g/dL. Overall, the cohort was considered medically fit for palliative chemotherapy; however, the majority were either malnourished or experiencing inflammation at the time of enrollment (Table 1).

3.1. Factors Associated With Advanced BMI-Adjusted BWL Grades in Patients With Recurrent/Metastatic HNC/NPC. We analyzed the potential factors linked to varying grades of BMI-adjusted BWL. Data on Table 2 indicate that patients with advanced grades (3 + 4) of BMI-adjusted BWL exhibited T3–4 tumor statuses more frequently than those with 0–2 grades. Moreover, they also showed higher eGFR, platelet count, CRP, and copper levels as well as lower levels of albumin, selenium, and TBARS. Multivariate analyses identified eGFR and copper levels as significant factors associated with advanced grades (3 + 4) of BMI-adjusted BWL (Table 3).

3.2. Factors Associated With LBM and TFM in Patients With Recurrent/Metastatic HNC/NPC. We performed univariate analyses to examine the relationships between various variables and both LBM and TFM. As detailed in Tables 4 and 5, LBM was significantly associated with ECOG performance status, positively correlated with TFM, uric acid, phosphorus, albumin levels, and negatively correlated with CRP, TNFα, IL-6, IL-8, and copper levels. Similarly, TFM was linked to dyslipidemia status, positively correlated with LBM, hemoglobin, total bilirubin, albumin, total cholesterol, triglycerides, and selenium levels, and negatively correlated with platelet count, and eGFR, CRP, IL-8, and copper levels.

Using non-parametric ANCOVA to assess the independent relationships of these variables with LBM and TFM, we identified significant correlations. Regarding LBM, significant associations were observed with TFM ($F(1, 66) = 13.353$, $p = 0.001$; partial $\eta^2 = 0.168$, large effect size), uric acid ($F(1, 66) = 6.908$, $p = 0.011$; partial $\eta^2 = 0.095$, medium-to-large effect size), phosphorus ($F(1, 66) = 7.205$, $p = 0.009$; partial $\eta^2 = 0.098$, medium-to-large effect size), and TNFα ($F(1, 66) = 6.829$, $p = 0.011$; partial $\eta^2 = 0.094$, medium-to-large effect size) after adjusting for covariates (Table 6).

Similarly, TFM showed significant associations with LBM ($F(1, 63) = 18.271$, $p = 0.001$; partial $\eta^2 = 0.225$, large effect size), copper levels ($F(1, 63) = 4.549$, $p = 0.037$; partial $\eta^2 = 0.067$, medium-to-large effect size), and zinc levels ($F(1, 63) = 4.723$, $p = 0.033$; partial $\eta^2 = 0.070$, medium-to-large effect size) (Table 7).

Figure 1 presents all statistically significant correlations identified through the preceding multivariate analysis.

4. Discussion

Understanding the factors contributing to malnutrition in patients with cancer is a crucial first step toward addressing this unmet medical need. Malnutrition is influenced by a variety of factors, including patient characteristics (e.g., sex assigned at birth, age, lifestyle, comorbidities, and performance status) and tumor-specific factors (e.g., type, location, involvement, and extent of spread). To minimize confounding variables, we focused on a homogeneous group of male patients with HNC or NPC who were preparing for palliative chemotherapy due to either newly diagnosed metastatic disease or first recurrence. This approach allowed us to control for variations in sex assigned at birth, tumor stage, and tumor type during our observational analysis. It also accurately identified the key determinants of malnutrition and clarified the relationships between body composition, patient factors, and tumor variables.

In the present study, after adjusting for covariates, we demonstrated that plasma copper levels are significantly associated with advanced grades of BMI-adjusted BWL. Specifically, plasma copper levels exhibit a negative correlation with BWL ($r = -0.486$, $p < 0.001$) and BMI ($r = -0.461$, $p < 0.001$). Additionally, BWL shows a positive association with both LBM ($r = 0.652$, $p < 0.001$) and TFM ($r = 0.652$,

Table 1: Baseline characteristics of the 78 male patients with recurrent/metastatic HNC and NPC included in this study.

Variables (expressed as *n* (%), percentage (%), and/or mean ± SD [median])	
Total number of participants	78
Age (years)	56.34 ± 9.45 (58.0)
ECOG PS (0:1:2)	6 (7.7):64 (82.1):8 (10.2)
Tumor sites	
Oral cavity	44 (56.4)
Oropharynx	11 (14.1)
Nasopharynx	11 (14.1)
Hypopharynx	7 (9.0)
Larynx	5 (6.4)
r/mTNM stage	
T0–2:T3–4	25 (32.1):53 (67.9)
N0–1:N2–3	31 (39.7):47 (60.3)
M0:M1	59 (75.6):19 (24.4)
Smoking exposure (%)	69.2
Alcohol consumption (%)	59.0
Betel quid use (%)	52.6
Comorbid illnesses	
Diabetes mellitus (%)	14.1
Hypertension (%)	24.4
Dyslipidemia (%)	19.2
COPD (%)	12.8
Anthropometric data	
BH (m)	1.66 ± 0.05 (1.67)
BW (kg)	58.17 ± 12.30 (55.30)
BMI (kg/m^2)	20.99 ± 3.92 (20.45)
< 18.5:≥ 18.5	26 (33.3):52 (67.7)
BWL (%)	−7.96 ± 18.30 (−6.93)
< 5:≥ 5	11 (14.1):67 (85.9)
Grade of BMI-adjusted BWL	
0:1:2:3:4	11 (14.1):24 (30.8):3 (3.8):5 (6.4)35 (44.9)
DXA-related measurements	
LBM (kg)	42.76 ± 6.42 (41.01)
TFM (kg)	12.75 ± 7.63 (11.17)
Biochemical data	
eGFR ($mL/min/1.73\ m^2$)	109.18 ± 30.50 (109.54)
≤ 60:> 60	2 (2.6):76 (97.4)
ALT (U/L; normal: ≤ 36)	27.69 ± 18.27 (22.00)
Bil-T (mg/dL; normal: ≤ 1.3)	0.38 ± 0.24 (0.30)
≤ 1.3:> 1.3 (%)	76 (97.4):2 (2.6)
Uric acid (mg/dL; normal: < 7.0)	4.77 ± 1.55 (4.20)
Fasting sugar (mg/dL)	104.32 ± 28.46 (96.00)
Nutrition-inflammation markers	
Hb (g/dL)	11.67 ± 1.89 (11.50)
WBC ($\times 10^3$ cells/mm^3)	9.26 ± 7.62 (7.50)
Platelet count ($\times 10^3/mm^3$)	279.84 ± 96.80 (285.00)
Albumin (g/dL; normal: 3.5–5.5)	3.81 ± 0.53 (3.85)
< 3.5:≥ 3.5	17 (21.8):61 (78.2)
TLC ($\times 10^3$ cells/mm^3)	1.03 ± 0.45 (1.00)
Total cholesterol (mg/dL; normal: < 200)	159.60 ± 42.03 (150.00)
Triglyceride (mg/dL; normal: < 150)	120.55 ± 110.55 (99.00)
CRP (mg/L)	25.57 ± 31.59 (17.48)
≤ 5:> 5	19 (24.4):59 (75.6)
Plasma cytokine levels	
TNFα (mM)	33.87 ± 52.75 (19.67)
IL-1β (mM)	8.73 ± 11.12 (2.99)
IFNγ (mM)	47.46 ± 76.03 (27.90)
IL-6 (mM)	23.46 ± 43.72 (5.20)
IL-8 (mM)	25.11 ± 52.39 (6.98)
VEGF (mM)	161.00 ± 161.50 (124.20)

Table 1: Continued.

Variables (expressed as *n* (%), percentage (%), and/or mean ± SD [median])	
Plasma minerals and trace element levels	
Calcium (mg/dL; normal: 8.6–10.3)	9.56 ± 0.89 (9.40)
Phosphorus (mg/dL; normal: 2.4–4.7)	3.55 ± 0.79 (3.60)
Magnesium (mEq/L; normal: 1.3–2.1)	1.61 ± 0.20 (1.60)
Magnesium < 1.3:≥ 1.3	6 (7.7):72 (92.3)
Sodium (mEq/L; normal: 136–146)	135.80 ± 3.52 (136.00)
Potassium (mEq/L; normal: 3.5–5.1)	4.27 ± 0.51 (4.30)
Chloride (mEq/L; normal: 102–112)	98.04 ± 5.57 (98.78)
Se (mg/L; normal: 60–170)	93.41 ± 23.11 (90.57)
Cu (mg/dL; normal: 62–140)	109.25 ± 25.17 (106.65)
Zn (mg/dL; normal: 66–110)	56.83 ± 20.02 (52.46)
Plasma antioxidant activity levels	
GPx (μmol/min/mL)	108.921 ± 74.32 (99.78)
SOD (U/mL)	2.40 ± 1.76 (2.12)
Catalase (nmol/min/mL)	112.70 ± 121.10 (75.81)
TBARS (mM)	8.16 ± 5.82 (6.82)

Note: ALT, alanine aminotransferase; Bil-T, total bilirubin; Cu, copper; DXA, dual-energy X-ray absorptiometry; GPx, glutathione peroxidase; Hb, hemoglobin; IFN, interferon; IL, interleukin; NPC, nasopharyngeal cancer; Se, selenium; SOD, superoxide dismutase; TBARS, thiobarbituric acid–reactive substances; Zn, zinc.

Abbreviations: BH, body height; BMI, body mass index; BW, body weight; BWL, body weight loss; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; ECOG PS, Eastern Cooperative Oncology Group performance status; eGFR, estimated glomerular filtration rate; HNC, head and neck cancer; LBM, lean body mass; SD, standard deviation; TFM, total fat mass; TLC, total lymphocyte count; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor; WBC, white blood cell.

Table 2: Clinical features, anthropometric data, biochemical data, nutrition-inflammation markers, plasma cytokine levels, plasma mineral and trace element levels, and plasma antioxidant activity levels in the 78 male patients with recurrent/metastatic HNC and NPC (stratified by grade of BMI-adjusted BWL).

	BMI-adjusted BWL		*p* value*
	0 + 1 + 2	3 + 4	
Variables (expressed as *n* (%), percentage (%), and/or mean ± SD)			
Number of participants	38	40	
Age (years)	58.39 ± 9.58	54.63 ± 9.14	0.097
ECOG PS			
0:1:2	5 (13.2):29 (76.3):4 (10.5)	1 (2.5):35 (87.5):4 (10.0)	0.204
Tumor sites			
Oral cavity: nonoral cavity	22 (57.9):16 (42.1)	21 (52.5):19 (47.5)	0.632
r/mTNM stage			
T0–2:T3–4	17 (44.7):21 (55.2)	8 (20.0):32 (80.0)	0.019*
N0–1:N2–3	18 (49.4):20 (52.6)	13 (32.5):27 (67.5)	0.180
M0:M1	28 (73.7):10 (26.3)	31 (77.5):9 (22.5)	0.695
Smoking exposure (%)	63.2	75.0	0.257
Alcohol consumption (%)	55.3	62.5	0.516
Betel quid use (%)	12.6	12.5	0.991
Comorbid illnesses			
Diabetes mellitus (%)	15.8	10.5	0.677
Hypertension (%)	31.6	17.5	0.148
Dyslipidemia (%)	18.4	20.0	0.860
COPD (%)	18.4	7.5	0.149
Anthropometric data			
BH (m)	1.67 ± 0.52	1.66 ± 0.57	0.452
BW (kg)	67.20 ± 11.10	49.61 ± 4.84	< 0.001*
BMI (kg/m^2)	24.11 ± 3.17	18.07 ± 1.51	< 0.001*
< 18.5:≥ 18.5	0 (0.0):38 (100.0)	26 (65.0):14 (35.0)	< 0.001*
BWL (%)	7.48 ± 10.15	−22.62 ± 10.52	< 0.001*
< 5:≥ 5	37 (97.4):1 (2.6)	0 (0.0):40 (100.0)	< 0.001*
DXA-related measurements			
LBM (kg)	45.67 ± 7.09	39.88 ± 4.03	< 0.001*
TFM (kg)	17.33 ± 6.00	8.57 ± 6.49	< 0.001*

Table 2: Continued.

	BMI-adjusted BWL		p value*
	0 + 1 + 2	3 + 4	
Biochemical data			
eGFR (mL/min/1.73 m^2)	98.71 ± 28.62	119.25 ± 28.76	0.002*
≤ 60:> 60	2 (5.3):36 (94.7)	0 (0.0):40 (100.0)	0.142
ALT (U/L; normal: ≤ 36)	26.87 ± 16.52	28.35 ± 19.77	0.721
Bil-T (mg/dL; normal: ≤ 1.3)	0.43 ± 0.29	0.33 ± 0.18	0.071
≤ 1.3:> 1.3	37 (97.4):1 (2.6)	39 (97.5):1 (2.5)	0.971
Uric acid (mg/dL; normal: < 7.0)	5.01 ± 1.83	4.39 ± 1.42	0.077
Fasting sugar (mg/dL)	108.31 ± 36.37	100.28 ± 10.55	0.212
Nutrition-inflammation markers			
Hb (g/dL)	12.11 ± 2.33	11.36 ± 1.54	0.091
WBC (× 10^3 cells/mm^3)	8.02 ± 3.43	10.34 ± 10.00	0.180
Platelet count (× 10^3/mm^3)	252.92 ± 93.58	303.00 ± 94.52	0.021*
Albumin (g/dL; normal: 3.5–5.5)	3.74 ± 0.51	3.69 ± 0.52	0.037*
< 3.5:≥ 3.5	4 (10.5):34 (89.5)	13 (32.5):27 (67.5)	0.019*
TLC (× 10^3 cells/mm^3)	1.03 ± 0.51	1.02 ± 0.48	0.094
Total cholesterol (mg/dL; normal: < 200)	162.29 ± 42.46	155.78 ± 42.15	0.489
Triglycerides (mg/dL; normal: < 150)	127.55 ± 107.82	123.25 ± 113.07	0.864
CRP (mg/L)	20.79 ± 23.91	33.48 ± 36.50	0.075
≤ 5:> 5	14 (36.8):24 (63.2)	5 (32.5):35 (87.5)	0.012*
Plasma cytokine levels			
TNFα (mM)	28.78 ± 40.77	38.17 ± 61.75	0.433
IL-1β (mM)	8.58 ± 11.81	8.91 ± 11.64	0.901
IFNγ (mM)	49.38 ± 81.35	44.55 ± 70.86	0.780
IL-6 (mM)	15.13 ± 25.59	30.81 ± 61.75	0.108
IL-8 (mM)	15.88 ± 31.59	33.27 ± 65.32	0.137
VEGF (mM)	154.05 ± 174.14	163.76 ± 152.40	0.794
Plasma mineral and trace element levels			
Calcium (mg/dL; normal: 8.6–10.3)	9.58 ± 0.90	9.50 ± 0.90	0.698
Phosphorus (mg/dL; normal: 2.4–4.7)	3.63 ± 0.69	3.45 ± 0.89	0.317
Magnesium (mEq/L; normal: 1.3–2.1)	1.61 ± 0.20	1.62 ± 0.21	0.712
Magnesium < 1.3:≥ 1.3	4 (10.5):34 (89.5)	39 (97.5):1 (2.5)	0.360
Sodium (mEq/L; normal: 136–146)	136.12 ± 3.91	135.60 ± 3.16	0.514
Potassium (mEq/L; normal: 3.5–5.1)	4.19 ± 0.43	4.33 ± 0.58	0.210
Chloride (mEq/L; normal: 102–112)	99.20 ± 6.16	97.02 ± 4.72	0.082
Se (mg/L)	98.35 ± 26.40	87.74 ± 19.06	0.044*
Cu (mg/dL)	97.58 ± 24.03	119.52 ± 21.75	< 0.001*
Zn (mg/dL)	60.27 ± 23.27	54.56 ± 17.08	0.219
Plasma antioxidant activity levels			
GPx (μmol/min/mL)	108.36 ± 68.96	107.80 ± 79.80	0.974
SOD (U/mL)	2.60 ± 1.87	2.22 ± 1.62	0.334
Catalase (nmol/min/mL)	119.84 ± 117.96	104.54 ± 123.85	0.578
TBARS (mM)	9.89 ± 6.90	6.56 ± 4.09	0.013*

Note: Nonparametric statistics with Mann–Whitney U test were used for analyzing BW, BMI, LBM, Hb, potassium, Se, TBARS, IL-6, and IL-8; an independent t test was used for other continuous variables. The chi-square test was used to analyze smoking, alcohol, betel quid, all comorbid illnesses, BWL (cutoff: 5%), BMI (cutoff: 18.5), eGFR (cutoff: 60), Bil-T (cutoff: 1.3), magnesium (cutoff: 1.3), albumin (cutoff: 3.5), and CRP (cutoff: 5). An analysis of variance (ANOVA) was used in the analysis of ECOG PS. ALT, alanine aminotransferase; Bil-T, total bilirubin; Cu, copper; DXA, dual-energy X-ray absorptiometry; GPx, glutathione peroxidase; Hb, hemoglobin; IFN, interferon: IL, interleukin; NPC, nasopharyngeal cancer; Se, selenium; SOD, superoxide dismutase; TBARS, thiobarbituric acid–reactive substances; Zn, zinc.

Abbreviations: BH, body height; BMI, body mass index; BW, body weight; BWL, body weight loss; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; ECOG PS, Eastern Cooperative Oncology Group performance status; eGFR, estimated glomerular filtration rate; HNC, head and neck cancer; LBM, lean body mass; SD, standard deviation; TFM, total fat mass; TLC, total lymphocyte count; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor; WBC, white blood cell.

*Value differences between BMI-adjusted BWL 0 + 1 + 2 and BMI-adjusted BWL 3 + 4 for each variable. $p < 0.05$ was considered statistically significant.

$p < 0.001$). Similarly, BMI demonstrates a strong positive correlation with both LBM ($r = 0.789$, $p < 0.001$) and TFM ($r = 0.790$, $p < 0.001$). Furthermore, univariate and multivariate analyses showed that plasma copper levels are inversely correlated with LBM and TFM, respectively. Although the relationship between copper and changes on BW and body composition in patients with cancer is complex and not fully understood, this comprehensive study demonstrates that malnutrition in patients with recurrent or metastatic HNC and NPC is associated with reduced levels

Table 3: Univariate and multivariate logistic regression analyses of those variables associated with 3 + 4 grades of BMI-adjusted BWL in 78 male patients with recurrent/metastatic HNC and NPC.

Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Tumor status (ref, T3-4)	0.309 (0.113–0.843)	0.022*		
Albumin (ref: ≥ 3.5 g/dL)	4.093 (1.197–13.892)	0.025*		
CRP (ref: > 5 mg/L)	0.245 (0.078–0.771)	0.016*		
eGFR	1.027 (1.008–1.046)	0.005*	1.021 (1.004–1.046)	0.018*
Platelets	1.006 (1.001–1.011)	0.026*		
Se	0.980 (0.960–1.000)	0.049*		
Cu	1.043 (1.019–1.069)	< 0.001*	1.041 (1.015–1.069)	0.002*
TBARS	0.899 (0.806–0.981)	0.020*		

Note: Cu, copper; NPC, nasopharyngeal cancer; Se, selenium; TBARS, thiobarbituric acid–reactive substances.
Abbreviations: BMI, body mass index; BWL, body weight loss; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; HNC, head and neck cancer; OR, odds ratio.
*$p < 0.05$ was considered statistically significant.

Table 4: Univariate associations (*p* values) between LBM and TFM with the clinical features and comorbidities of 78 male patients with recurrent/metastatic HNC and NPC.

	Patient number	LBM (kg)	*p* value	TFM (kg)	*p* value
Clinical feature					
ECOG PS			0.020*		0.535
0	6	47.99 ± 7.00		15.39 ± 6.81	
1	64	42.74 ± 6.31		12.39 ± 6.85	
2	8	38.46 ± 3.49[a]		14.50 ± 13.13[b]	
Cancer sites			0.419		0.826
Oral cavity	43	42.14 ± 4.82		13.01 ± 7.95	
Nonoral cavity	35	43.39 ± 7.94		12.62 ± 7.30	
T extent			0.309		0.089
T0–2	25	43.78 ± 6.14		14.98 ± 6.88	
T3–4	53	42.19 ± 6.51		11.85 ± 7.80	
N involvement			0.538		0.373
N0–1	31	42.15 ± 5.27		13.78 ± 9.01	
N2–3	47	43.06 ± 7.07		12.21 ± 6.57	
Metastatic status			0.306		0.571
M0	59	42.28 ± 5.39		12.56 ± 7.50	
M1	19	44.02 ± 9.08		13.71 ± 7.32	
Smoking			0.303		0.428
No	24	43.83 ± 5.71		13.87 ± 6.90	
Yes	54	42.20 ± 6.67		12.38 ± 7.93	
Alcohol			0.587		0.608
No	32	42.83 ± 5.26		12.37 ± 8.24	
Yes	46	42.61 ± 7.54		12.47 ± 7.22	
Betel quid			0.857		0.7881
No	37	42.56 ± 5.00		13.09 ± 7.90	
Yes	41	42.83 ± 7.51		12.61 ± 7.44	
Hypertension			0.969		0.434
No	59	42.72 ± 6.96		12.45 ± 7.80	
Yes	19	42.65 ± 4.38		14.03 ± 7.09	
Diabetes mellitus			0.498		0.922
No	67	42.90 ± 6.44		12.87 ± 8.00	
Yes	11	41.48 ± 6.27		12.63 ± 4.90	

Table 4: Continued.

	Patient number	LBM (kg)	*p* value	TFM (kg)	*p* value
COPD			0.684		0.585
No	68	42.59 ± 6.60		12.66 ± 7.77	
Yes	10	43.48 ± 5.04		14.08 ± 6.73	
Dyslipidemia			0.845		0.006*
No	63	42.77 ± 6.48		11.69 ± 6.55	
Yes	15	42.41 ± 6.24		17.67 ± 7.91	

Note: Independent student's *t*-tests were used to analyze T extent, N involvement, metastatic status, smoking, alcohol, betel quid, hypertension, diabetes mellitus, COPD, and dyslipidemia associations with HNC/NPC. An analysis of variance was done to ECOG PS data (0 vs. 1 vs. 2). M, metastasis; N, nodal involvement; NPC, nasopharyngeal cancer; T, tumor extent.

Abbreviations: COPD, chronic obstructive pulmonary disease; ECOG PS, Eastern Cooperative Oncology Group performance status; HNC, head and neck cancer; LBM, lean body mass; TFM, total fat mass.

*$p < 0.05$ was considered statistically significant.

[a]Comparison between ECOG 0 and ECOG 2 ($p < 0.05$).

[b]Comparison between ECOG 1 and ECOG 2 ($p < 0.05$).

Table 5: Correlation associations (*p* values) of LBM and TFM with the clinical features, biochemical data, nutrition-inflammation markers, serum cytokine levels, and serum antioxidant activity levels of 78 male patients with recurrent/metastatic HNC and NPC.

	LBM	TFM
Clinical feature		
Age	0.086	0.087
DXA-related measurement		
LBM	—	< 0.001*
TFM	< 0.001*	—
Biochemical data		
eGFR	0.506	0.010*
ALT	0.819	0.533
Bil-T	0.829	0.021*
Uric acid	0.032*	0.202
Fasting sugar	0.423	0.492
Nutrition-inflammation markers		
Hb	0.287	0.005*
WBC	0.676	0.375
TLC	0.180	0.364
Platelet count	0.656	0.001*
Albumin	0.046*	0.001*
Total cholesterol	0.411	0.010*
Triglyceride	0.396	0.040*
CRP	0.004*	0.004*
Plasma cytokines		
TNFα	0.006*	0.052
IL-1β	0.098	0.749
IFNγ	0.815	0.234
IL-6	0.003*	0.078
IL-8	0.048*	0.031*
VEGF	0.617	0.213
Plasma mineral and trace elements		
Calcium	0.148	0.184
Phosphorus	0.010*	0.417
Magnesium	0.090	0.792
Sodium	0.429	0.637
Potassium	0.180	0.097
Chloride	0.250	0.686
Selenium	0.150	0.002*
Copper	0.007*	< 0.001*
Zinc	0.999	0.019*
Plasma antioxidant activity		
GPx	0.773	0.068
SOD	0.405	0.068
Catalase	0.664	0.616
TBARS	0.459	0.078

Note: Univariate associations were determined using correlation analyses. ALT, alanine aminotransferase; Bil-T, total bilirubin; DXA, dual-energy x-ray absorptiometry; GPx, glutathione peroxidase; Hb, hemoglobin; IFN, interferon; IL, interleukin; NPC, nasopharyngeal cancer; SOD, superoxide dismutase; TBARS, thiobarbituric acid–reactive substances.

Abbreviations: CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; HNC, head and neck cancer; LBM, lean body mass; TFM, total fat mass; TLC, total lymphocyte count; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor; WBC, white blood cell.

*$p < 0.05$ indicates statistical significance.

of both LBM and TFM, which may be linked to increased plasma copper levels.

Since copper plays a critical role in regulating energy utilization and maintaining overall metabolic pathways, the reverse association between copper and malnutrition in patients with cancer could be explained as follows. First, increased copper levels may stimulate the production of proinflammatory cytokines, such as IL-6, IL-8, and TNF-α [42]. These cytokines drive ROS production, exacerbate oxidative stress, and promote muscle and fat catabolism [43–45]. This hypothesis is partially supported by our study findings, which reveal positive correlations between copper and IL-6 ($r = 0.304$, $p = 0.007$), IL-8 ($r = 0.243$, $p = 0.032$), and TNF-α ($r = 0.304$, $p = 0.007$). Additionally, significant correlations were observed between CRP and IL-6 ($r = 0.326$, $p = 0.004$) as well as with TNF-α ($r = 0.381$, $p = 0.001$). Conversely, negative correlations were observed between LBM and CRP ($r = -0.320$, $p = 0.004$), IL-6 ($r = -0.332$, $p = 0.003$), TNF-α ($r = -0.308$, $p = 0.005$), and IL-8 ($r = -0.225$, $p = 0.042$). Moreover, TFM also showed negative correlations with CRP ($r = -0.323$, $p = 0.004$) and IL-8 ($r = -0.245$, $p = 0.031$).

Table 6: LBM association analysis from 78 male patients with recurrent/metastatic HNC and NPC.

Sources of variation	Sum of squares	df	Mean square	*F* value	*p* value	Partial η^2
ECOG PS	1569.814	2	784.907	2.583	0.083	0.073
TFM	4057.153	1	4057.153	13.353	0.001*	0.168
Albumin	852.852	1	852.852	2.807	0.099	0.041
CRP	2.382	1	2.382	0.008	0.930	0.000
Uric acid	2098.854	1	2098.854	6.908	0.011*	0.095
Phosphorus	2189.112	1	2189.112	7.205	0.009*	0.098
TNFα	2074.934	1	2074.934	6.829	0.011*	0.094
IL-6	715.944	1	715.944	2.352	0.130	0.034
IL-8	403.807	1	403.807	1.329	0.253	0.020
Copper	13.837	1	13.837	0.046	0.832	0.001
Error	20,052.886	66	303.832			
Total	161,239.000	78				

Note: IL, interleukin; NPC, nasopharyngeal cancer.
Abbreviations: CRP, C-reactive protein; df, degrees of freedom; ECOG PS, Eastern Cooperative Oncology Group performance status; HNC, head and neck cancer; LBM, lean body mass; TFM, total fat mass; TNF, tumor necrosis factor.
* $p < 0.05$ indicates statistical significance.

Table 7: TFM association analysis from 78 male patients with recurrent/metastatic HNC and NPC.

Sources of variation	Sum of squares	df	Mean square	*F* value	*p* value	Partial η^2
Dyslipidemia	996.116	1	996.116	3.557	0.064	0.053
LBM	5117.391	1	5117.391	18.271	0.001*	0.225
Albumin	610.232	1	610.232	2.179	0.145	0.033
CRP	555.125		555.125	1.982	0.164	0.031
Hb	152.543	1	152.543	0.545	0.463	0.009
Platelet	125.410	1	125.410	0.448	0.506	0.007
Total cholesterol	0.931	1	0.931	0.0003	0.904	0.000
Triglyceride	140.399	1	140.399	0.501	0.482	0.008
eGFR	74.444	1	74.444	0.266	0.608	0.004
Bil-T	610.232	1	610.232	2.179	0.145	0.033
IL-8	60.611	1	60.611	0.216	0.643	0.003
Selenium	116.697	1	116.697	0.417	0.521	0.007
Copper	1274.110	1	1274.110	4.549	0.037*	0.067
Zinc	1323.813	1	1323.813	4.727	0.033*	0.070
Error	17,644.999	63	280.079			
Total	161,239.000	78				

Note: Bil-T, total bilirubin; Hb, hemoglobin; IL, interleukin; NPC, nasopharyngeal cancer.
Abbreviations: CRP, C-reactive protein; df, degrees of freedom; eGFR, estimated glomerular filtration rate; HNC, head and neck cancer; LBM, lean body mass; TFM, total fat mass.
* $p < 0.05$ indicates statistical significance.

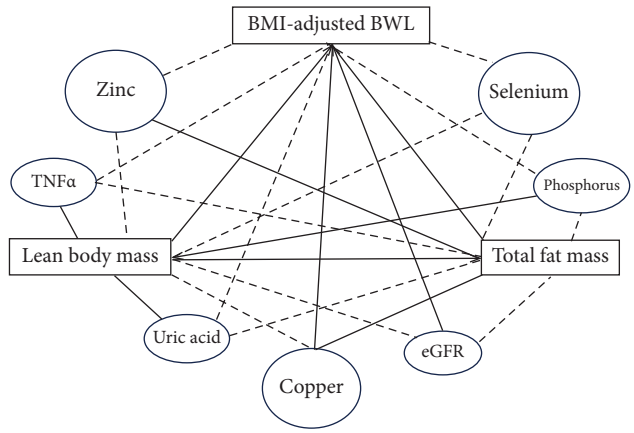

Figure 1: Correlation network among BMI-adjusted body weight loss (BMI-adjusted BWL), lean body mass, total fat mass, selenium, copper, zinc, and relevant clinical variables. Solid lines represent statistically significant correlations between two variables ($p < 0.05$), while dashed lines indicate nonsignificant associations. TNFα: tumor necrosis factor-alpha. eGFR: estimated glomerular filtration rate.

Second, elevated copper levels enhance mitochondrial activity and oxidative metabolism via cytochrome c oxidase, increasing the basal metabolic rate and energy expenditure, leading to weight loss [46, 47]. Besides, elevated copper levels may activate lipase activity and promote fat breakdown, while disrupting glucose metabolism and insulin signaling [48]. These effects further impair energy utilization and contribute to malnutrition. Elevated copper levels may also activate muscle proteolysis through the ubiquitin-proteasome system and inhibit muscle synthesis by interfering with anabolic signaling pathways, such as the insulin-like growth factor-1 signaling pathway [49, 50]. Furthermore, tumor cells exploit systemic copper to enhance angiogenesis [51] and accelerate proliferation. These processes collectively increase inflammation, oxidative stress, and metabolic demands, while depleting nutritional resources, ultimately leading to weight loss and cachexia. Together, these copper-mediated mechanisms contribute to malnutrition and alterations in body composition in patients with cancer. An alternative hypothesis linking copper levels, malnutrition, and body composition is that cancer-induced inflammation and oxidative stress elevate plasma copper levels [52], promoting muscle breakdown and fat tissue loss.

In addition to copper, plasma phosphorus levels showed a positive correlation with LBM, and plasma zinc levels were positively linked to TFM. These findings align with previous reports highlighting the close relationship between mineral levels, malnutrition, and body composition [20–23, 26, 27]. Phosphorus is critical for cellular energy metabolism and skeletal muscle function. Adequate phosphorus levels support the production of adenosine triphosphate—the primary energy source for muscle repair—phosphocreatine storage, which provides rapid energy during high-intensity activities, and protein synthesis, essential for muscle growth[53, 54]. In this study, the phosphorus levels of patients with cancer were within the normal range and observed a positive correlation with albumin ($r = 0.298$, $p = 0.008$). These results support the link between phosphorus and LBM.

Similarly, zinc is essential in adipogenesis, lipid metabolism, and energy regulation [55–57]. Increased zinc levels improve insulin sensitivity and leptin production, enhancing glucose uptake and fat storage [58]. In addition, zinc mitigates inflammation and oxidative stress, indirectly facilitating fat accumulation [59]. Zinc can modulate signaling pathways in white adipose tissue to promote fat deposition [60]. In this study, plasma zinc levels were positively correlated with albumin ($r = 0.427$, $p < 0.001$) but showed no association with CRP or cytokine concentrations. These results suggest that the relationship between zinc and TFM may involve direct effects on lipogenesis, rather than indirect effects on other pathways, through inflammation reduction.

Several findings from this study should be highlighted and merit further discussion. In the studied cohort, those patients with cancer with advanced BMI-adjusted BWL exhibited higher eGFRs, and both BMI ($r = -0.342$, $p = 0.002$) and BWL ($r = -0.342$, $p = 0.002$) were inversely correlated with eGFR. We hypothesize that the apparent overestimation of kidney function may stem from severe BWL, particularly in cases of cancer-related muscle wasting. This condition markedly lowers serum creatinine levels, resulting in a falsely elevated eGFR. Additionally, we observed a positive correlation between plasma uric acid levels and LBM. This finding could be attributed to muscle turnover, given that muscle cells are rich in purines and uric acid is a byproduct of purine metabolism. However, we do not support the hypothesis that uric acid acts as an antioxidant to neutralize free radicals and protect muscles from oxidative stress, as our study found no association between uric acid levels and inflammatory markers such as CRP or cytokines. Notably, half of participants in the cohort exhibited severe malnutrition (grades 3 + 4 of BMI-adjusted BWL), with nearly 90% experiencing a BWL greater than 5%. This suggests a significant energy deficit among patients with recurrent or metastatic HNC or NPC, likely resulting from insufficient food intake or a hypermetabolic state driven by cancer-induced inflammation and oxidative stress [61]. Such energy deficits are commonly observed in patients with HNC at time of diagnosis [62]. This energy deficit leads to compulsory depletion of both fat stores and muscle tissue to supply the body with free fatty acids, amino acids, and other nutrients needed for energy production, to meet metabolic demands. Additionally, an energy deficit reduces insulin and testosterone secretion and increases cortisol production, leading to decreases in muscle synthesis and muscle breakdown promotion. The present study revealed a positive and reciprocal association between LBM and total TFM, along with negative correlations between CRP and both LBM and TFM, indirectly supporting this hypothesis.

This study had several limitations. While factors associated with malnutrition, LBM, and TFM were observed, causal relationships were not established. Variations in the data used to assess nutritional status, inflammation severity, mineral concentrations, and body composition may have increased due to differences in measurement tools, biological specimens, and ethnicity. Especially, various methods for assessing body composition, such as computed tomography (CT) and bioelectrical impedance analysis (BIA), are well documented in clinical practice. While CT is a gold standard method, it involves higher radiation exposure and cost, and is less accessible than DXA. BIA is a convenient, low-cost, and radiation-free method, but its accuracy is affected by hydration, recent food intake, and population-specific factors, often overestimating fat-free mass and body fat, particularly at BMI extremes. In contrast, DXA offers more reliable measurements across diverse populations and clinical conditions [63]. Consequently, the results should be interpreted with caution. Additionally, key information, such as dietary records, medications, and other critical micronutrients that could interact with copper and influence inflammation and oxidative stress, was not included in the analysis. Finally, large-scale prospective studies are needed to validate these findings across various cancer types.

5. Conclusions

Addressing malnutrition remains an unmet medical need for patients with cancer. This cross-sectional study analyzed potential confounding factors and demonstrated that plasma

copper levels are associated with malnutrition, muscle mass, and fat storage in patients with recurrent or metastatic HNC or NPC undergoing palliative chemotherapy. In cancer patients experiencing malnutrition, assessing their nutritional and inflammatory status is a standard approach aimed at identifying and addressing underlying causes. However, imbalances in blood electrolyte and trace element levels—such as alterations in plasma copper—are often overlooked. The findings of this study suggest that measuring plasma copper concentrations may provide valuable insights into the etiology of malnutrition and associated changes in body composition among cancer patients in daily practice. Therefore, an effective management of plasma copper levels may help improve the nutritional status of patients with cancer.

Data Availability Statement

The data presented in this study are available upon request from the corresponding author.

Ethics Statement

The study was conducted in accordance with the guidelines of the Declaration of Helsinki and approved by the Institutional Review Board of Chang Gung Memorial Hospital (IRB approval number: 201601395A3C506, Date of approval: 2017).

Consent

Written informed consent was obtained from all subjects involved in the study.

Disclosure

All authors read and agreed to the published version of the manuscript.

Conflicts of Interest

The authors declare no conflicts of interest.

Author Contributions

Kun-Yun Yeh contributed to conceptualization. Kun-Yun Yeh, Hang Huong Ling, and Pei-Hung Chang performed data curation. Chun-Feng Wu, Kun-Yun Yeh, and Yi-Ping Pan carried out formal analysis. Kun-Yun Yeh and Pei-Hung Chang contributed to funding acquisition. Chun-Feng Wu, Kun-Yun Yeh, and Yu-Ching Lin conducted investigation. Kun-Yun Yeh, Chia-Lin Peng, and Zih-Syuan Chen contributed to methodology. Kun-Yun Yeh, Pei-Hung Chang, and Simon Hsia performed project administration. Kun-Yun Yeh and Simon Hsia provided resources and supervised the study. Kun-Yun Yeh provided software. Chun-Feng Wu, Kun-Yun Yeh, and Wen-Chi Chou performed validation. Kun-Yun Yeh, Wen-Chi Chou, and Yu-Ching Lin contributed to visualization. Chun-Feng Wu and Kun-Yun Yeh performed writing–original draft. Kun-Yun Yeh performed writing–review & editing.

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