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Original Article

Investigating sarcopenia, physical activity, and inflammation biomarkers in newly diagnosed oral cancer patients during curative treatment: A prospective longitudinal study

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ABSTRACT

Objective: This prospective longitudinal study aimed to investigate changes in sarcopenia, physical activity, and inflammation biomarkers in patients with oral cavity cancer during curative treatment and explore their association with treatment outcomes.

Methods: Patients newly diagnosed with oral cavity cancer who underwent primary surgery with (chemo)radiation therapy were included. Along with physical activity and inflammatory markers, sarcopenia was assessed using a 5-time chair stand test, hand grip strength, and skeletal muscle index (SMI). Data were collected before operation and after 3 months (T_2) and 6 months after operation. Logistic regression and Cox proportional hazards models were used to identify predictors of treatment outcomes.

Results: Out of 56 patients, 21 (37.5%) had sarcopenia. SMI score, physical activity, and neutrophil-to-lymphocyte ratio (NLR) showed significant changes after surgery, with exacerbation at T_2. Patients with sarcopenia exhibited a significant decrease in SMI scores at T_2. Advanced cancer stage and sarcopenia were associated with treatment-related dysphagia (odds ratio [OR] = 3.01, $P = 0.034$; OR = 7.62, $P = 0.018$). Sarcopenia (OR = 3.02, $P = 0.002$) and NLR (OR = 5.38, $P < 0.001$) were significantly associated with infections. Pretreatment SMI independently predicted poor survival outcomes (hazard ratio = 7.00, $P = 0.005$).

Conclusions: Identifying patients with oral cavity cancer, sarcopenia, and high NLR levels can ensure prompt education and vigilant monitoring, potentially improving treatment outcomes and patient well-being during curative treatment.

Introduction

Head and neck cancer (HNC) is the third most common cancer in Taiwan and the fifth leading cause of cancer-related death in men.[1] Taiwan has a considerably high incidence and prevalence of oral cavity cancer (OCC) within the spectrum of HNC.[2] According to the guidelines from the National Comprehensive Cancer Network, curative surgery is the primary treatment for OCC. The decision to administer postoperative (chemo)radiation for OCC is based on risk factors, such as tumour staging and the extent of pathological invasion identified in pathological examination.[3] In Taiwan, approximately 67% of patients with oral cancer are diagnosed in the advanced stage and require postoperative adjuvant therapy.[4] Nurses play a critical role in facilitating patients' smooth transition through perioperative and (chemo)radiation therapy. A comprehensive understanding of potential complications and toxicities is essential for optimal care and improved quality of life.[5,6]

In addition to the Tumor-Node-Metastasis criteria, human papillomavirus status, and patient characteristics, several factors, including age, nutritional status, and biological inflammatory status, can affect the treatment outcomes in OCC.[7] Sarcopenia, a progressive skeletal muscle disorder involving loss of muscle mass and function,[8] is a crucial factor in cancer cachexia. Skeletal muscle depletion is a common indicator of malnutrition related to cancer, and it may contribute to the progression of sarcopenia.[9] In addition to evaluating skeletal muscle mass, the assessment of skeletal muscle function is crucial and should be the focus of nutritional interventions, as recommended by the Global Leadership Initiative on Malnutrition.[10] Sarcopenia is a predictor of poor outcomes in various treatments for HNC.[11] These negative outcomes include

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chemotherapy-related toxicities,[12] high risk of postoperative complications,[13] early treatment discontinuation,[14] and increased mortality rates.[12,15] Additionally, patients undergoing (chemo)radiation therapy often encounter notable decreases in skeletal muscle mass, muscle strength, physical activity (PA) levels, fatigue regulation, and overall quality of life during and after the treatment course.[16] A previous study[17] reported that 8.5% of patients with HNC attained the recommended levels of exercise following their treatment. In HNC patients, higher self-perceived levels of PA have been linked to improved health-related quality of life and reduced fatigue compared to lower self-perceived PA levels.[18,19] However, understanding of the relationship between PA levels and treatment outcomes in patients with OCC is limited.

Accumulating meta-analysis evidence suggests that systemic inflammation is a negative predictive and prognostic factor in patients with OCC.[20,21] The pathophysiology of cancer extensively involves the modulation of the immune system, which plays a critical role in cancer cell growth, proliferation, and tumor development.[22] Systemic inflammatory response observed in cancer progression exerts significant catabolic effects on host metabolism, resulting in muscle breakdown and initiating a vicious cycle wherein progressive decline in muscle mass contributes to local inflammation, which in turn promotes further muscle breakdown and drives the systemic inflammatory response cascade.[23,24] The magnitude of inflammation can be indirectly explored via the measurement of systemic inflammation-based indicators, such as lymphocyte-to-monocyte ratio (LMR), neutrophil-to-lymphocyte ratio (NLR), and systemic immune-inflammation index (SII).[20,21] Despite extensive investigation through multiple systematic reviews and meta-analyses, the association between sarcopenia,[11,25,26] inflammation biomarkers,[20,21] and complications of HNC surgery, as well as the acute and late toxicity and adverse events (AEs) of (chemo)radiation, remains an area of ongoing research. Moreover, the influence of acute effects of cancer treatment on the progression of sarcopenia and inflammation biomarkers before and after cancer diagnosis remains uncertain. Furthermore, the relationship between changes in sarcopenia, PA, and inflammation biomarkers during treatment and their association with treatment of AEs and survival in patients with OCC is poorly established.

To address the gaps in the existing literature, the present study mainly aimed to investigate the changes in sarcopenia indices (ie, skeletal muscle mass, muscle strength, and physical performance), PA, and inflammation biomarkers in patients with OCC before and after curative-intent treatment. It also explored the relationship between these sarcopenia indices and inflammation biomarkers and their association with the development of treatment-related AEs in patients with OCC. Subsequently, the association between significant risk factors and survival was examined.

Methods

Study design and participants

This study utilized a prospective longitudinal design and recruited participants from hospital wards and outpatient clinics at an academic medical center in eastern Taiwan. Eligible participants were newly diagnosed with OCC, aged 20 years or above, and scheduled to receive curative treatment with surgical resection followed by adjuvant (chemo) radiation. They were required to be able to speak or read Mandarin and willing to provide informed consent for this study. Purposive sampling was used for participant recruitment. The exclusion criteria were as follows: having metastasis and a history of malignancy, having a second primary tumor, and having concurrent uncontrolled medical conditions or active infection.

Sample size

In our study, we used the generalized estimating equation (GEE) model to analyze the changes in sarcopenia, physical activity, and inflammation biomarkers among OCC patients undergoing primary tumor surgery with adjuvant (chemo)radiotherapy. The GEE model was selected for its advantages over repeated-measures Analysis of Variance (ANOVA) methods. Unlike ANOVA, the GEE model does not assume a normal distribution of the outcome variable, nor does it require constant variance and correlation between time points. In addition, it allows for the inclusion of patients with missing observations at different time points.[27] The required sample size was calculated using G-Power 3.1.9[28] based on repeated-measures ANOVA within-factors procedure with an f^2-value of 0.25, an α-value of 0.05, a desired power of 0.80, and a measurement number of 3. The sample size of 54 showed sufficient power (=1).

Ethics and treatment details

The study protocol was approved by the institutional review board (IRB) and research ethics committee of Hualien Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation (IRB No.109-183-B), and informed consent was obtained from the patients prior to participation. The study was conducted by recruiting patients between November 1, 2020, and February 28, 2022, and their survival status was followed-up until October 1, 2022. In the case of withdrawal, consultation and measurements were discontinued. All patients were treated by surgery excision or free-flap reconstruction with or without neck dissection (based depth of invasion). Postoperative adjuvant therapy was discussed by a multidisciplinary team to determine the most appropriate treatment for the patients, and performance status and risk factors were considered.[29] Adjuvant therapies, including radiation therapy, was initiated within 6 weeks after surgery.[30] Adjuvant radiation therapy was administered via an intensity-modulated radiotherapy approach at a total dose of 60 to 66 Gy, given in each fraction of 2 Gy per day, 5 days per week, either alone or concurrently with chemotherapy. Additionally, a prophylactic dose of 54 to 60 Gy was administered to the undissected neck nodal region at risk.[31,32] The chemotherapy regimen consisted of 20 mg/m^2 cisplatin administered on days 1–5 at 3- to 4-week intervals with or without oral tegafur–uracil (each capsule containing 100 mg of tegafur and 224 mg of uracil) with 3–6 daily capsules in 2–3 divided doses.[30] Prophylactic antibiotics, specifically cefmetazole, were administered 30 min before surgery and were continued for 7 days after operation at the discretion of the operating surgeon. During the adjuvant therapy period, patients with neutropenia did not receive antibacterial prophylaxis for preventing infections.[33]

Study procedure

In order to evaluate the acute to recovery phase, the study chose three time points for assessment. Primary outcomes, which included sarcopenia indices, physical activity levels, and inflammation biomarkers, were collected at baseline (1 to 3 days before the surgery, T_1), at 3 months (4 to 5 weeks after the start of radiotherapy, T_2), and 6 months after the surgery (completion of radiotherapy, T_3) to describe the changes over time. Secondary outcomes of treatment-related AEs were monitored, and the effects of demographics, disease characteristics, sarcopenia, PA levels, and inflammation biomarkers on treatment-related AEs were explored. Subsequently, the significant risk factors identified in the clinical and analytical findings were subjected to further analysis to investigate their correlation with survival outcomes. Data on demographics and clinical characteristics were collected at T_1 only. A research nurse was responsible for informing eligible participants about the study and screening potential patients by reviewing electronic medical records and confirming the treatment plan with the clinical physician.

Data collection and measurements

Demographic and clinical characteristics

Demographic data included age, gender, and history of smoking, alcohol consumption, and betel nut chewing. Clinical characteristics were extracted from electronic medical records, covering Charlson comorbidity index, cancer site, cancer stage, and treatment modality.

Sarcopenia incises

Sarcopenia was determined using the 2019 Asian Working Group for Sarcopenia (AWGS) guidelines,[34] which utilised skeletal muscle index (SMI), handgrip strength (HGS), and 5-time chair stand test (5-CST) as cutoff values. Severe sarcopenia was defined by reduced muscle mass, strength, and physical performance. Sarcopenia was defined by low muscle mass and/or strength. Appendicular skeletal muscle mass and appendicular SMI were assessed using bioelectrical impedance analysis (InBody S10, Biospace Co., Ltd., Seoul, Korea). The cutoff values for SMI were set at < 5.7 kg/m^2 for men and < 7.0 kg/m^2 for women. HGS was measured twice for each hand using a Smedley hand dynamometer (TKK 5401, Takei Scientific Instruments Co., Ltd., Tokyo, Japan) while the subject was standing, and the highest value of the four measurements was recorded as muscle strength. The cutoff value for HGS was set at $<$ 28 kg for men and at $<$ 18 kg for women. The 5-CST measured the time taken for a participant to complete 5 chair stands with arms crossed over the chest as quickly as possible, with a cutoff value of 12 s for physical performance.

Physical activity level

PA levels were assessed using the Taiwanese version of the International Physical Activity Questionnaire-Short Form, which was authorized by the Health Promotion Administration at the Ministry of Health and Welfare in Taiwan.[35] The participants were asked to report their PA levels for the previous 7 days, including four specific activity types: vigorous-intensity activities (eg, running and aerobics), moderate-intensity activities (eg, leisure cycling), walking and sitting that were performed during work, transport, housework, or leisure activities. The total score was calculated by adding the duration and frequency of walking and moderate- and vigorous-intensity activities, which was reported as the 'metabolic equivalent of task-min per week'. According to the IPAQ guidelines,[36] International Physical Activity Questionnaire-Short Form scores of $<$ 600, 600–3000 and $>$ 3000 metabolic equivalent of task -min/week were classified as low, moderate, and high PA levels. In consideration of previous research,[37] we classified PA levels into 2 distinct groups: low PA and moderate to high PA.

Inflammation biomarkers

The participants' blood samples were collected during routine blood exams at hospitalisation (T_1 and T_2) and clinical outpatient visits (T_3). We recorded the results of albumin, white blood cell count, haemoglobin, platelet count, and differential white blood cell count. Blood inflammation biomarkers, including LMR, NLR, and SII, were assessed as the ratio of lymphocyte count to the absolute count of monocytes and neutrophil count to lymphocyte count, respectively. SII was determined using the following equation: NLR $\times$ platelet count.

Treatment-related adverse events and survival follow-up

Patients were assessed for surgery-related complications using the Dindo system,[38] which categorizes complications into local-to-systemic categories within 30 days after surgery. Major complications were defined as a score of $\geq$ 3. Acute toxicity related to (chemo)radiation therapy was monitored weekly using the Common Terminology Criteria for Adverse Events (version 5.0).[39] Nutritional status and support requirements of patients were also assessed, and counseling was conducted every week by a dietician. Tube-feeding through a nasogastric tube was recommended for patients with significantly decreased oral intake or $\geq$ grade-3 dysphagia. The incidence of infection events within the first 6 months following the date of operation was documented. Infections within the first 6 months following the surgery were documented and were defined as the presence of positive bacterial or fungal cultures obtained from blood, sputum, urine, or surgical site wounds. In cases of

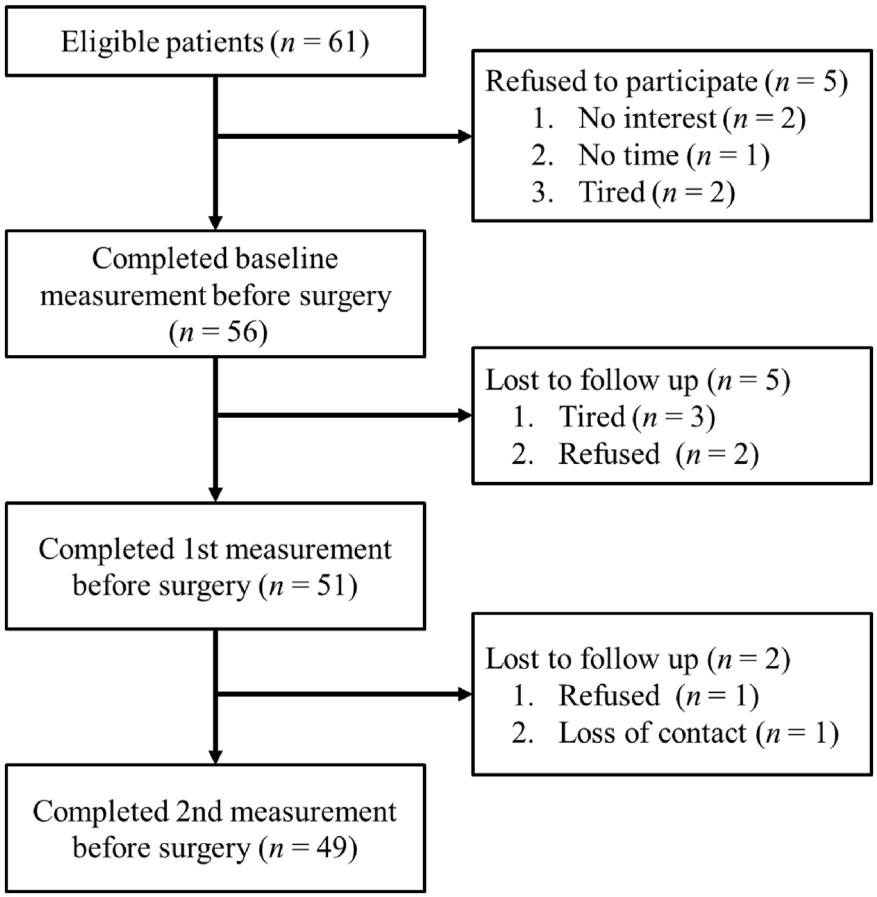

Fig. 1. Flow diagram of this study.

multiple positive cultures for the same organism, infection events were considered independent if they occurred within 30-day intervals. For polymicrobial infections, each isolated causative organism was considered a separate infection event. The patients were followed-up further until death or October 1, 2022, whichever occurred first. Overall survival (OS) was defined as the time from diagnosis until death due to any cause. Disease-free survival (DFS) was defined as the time from the date of diagnosis to the date of first relapse, progression, or death due to any cause. The relevant treatment-related AEs and survival outcomes were extracted from electronic medical records.

Data analysis

All statistical analyses were performed using the SPSS 28.0 program (SPSS Inc., Chicago, IL, USA). Quantitative variables were described as mean ± standard deviation. For variables with a skewed distribution,

Table 1
Demographic profile ($N = 56$).

Variables	Sarcopenia ($n = 21$), n (%)	Nonsarcopenia ($n = 35$), n (%)	$z/t/x^2$	P value
Age, years[a,b]	63.7 ± 9.6	58.5 ± 9.6	−1.945	0.862
< 65	10 (47.6)	24 (68.6)	2.416	0.120
≥ 65	11 (52.4)	11 (31.4)		
Gender[b]				
Male	19 (90.5)	29 (82.9)	0.622	0.430
Female	2 (9.5)	6 (17.1)		
Alcohol[b]				
Never	6 (28.6)	11 (31.4)	0.622	0.733
Former	4 (19.0)	4 (11.4)		
Current	11 (52.4)	20 (57.1)		
Smoking[b]				
Never	5 (23.8)	10 (28.6)	0.565	0.754
Former	6 (28.6)	7 (20.0)		
Current	10 (47.6)	18 (51.4)		
Betel nut[b]				
Never	5 (23.8)	12 (34.3)	0.735	0.693
Former	3 (14.3)	5 (14.3)		
Current	13 (61.9)	18 (51.4)		
CCI[b]				
< 5	14 (66.7)	28 (80.0)	1.244	0.265
≥ 5	7 (33.3)	7 (20.0)		
Cancer site[b]				
Buccal mucosa	9 (42.9)	14 (40.0)	1.128	0.890
Lower gum	6 (28.6)	11 (31.4)		
Tongue	3 (14.3)	3 (8.6)		
Lower lip	1 (4.8)	4 (11.4)		
Other sites	2 (9.5)	3 (8.6)		
Pathologic stage[b]				
I	0 (0)	6 (17.1)	4.393	0.222
II	4 (19.1)	5 (14.3)		
III	7 (33.3)	8 (22.9)		
IV	10 (47.6)	16 (45.7)		
BMI, kg/m^2[a,b]	22.5 ± 4.1	26.0 ± 5.7	2.463	0.387
< 18.5	10 (47.6)	18 (51.4)	2.616	0.270
18.5–24.9	3 (14.3)	1 (2.9)		
≥ 25.0	8 (38.1)	16 (45.7)		
Albumin, g/dL[a,b]	3.6 ± 0.6	3.7 ± 0.5	0.259	0.797
≥ 3.5	14 (66.7)	23 (65.7)	0.062	0.804
< 3.5	7 (33.3)	12 (34.3)		
Hb, g/dL[a,b]	11.0 ± 1.9	11.5 ± 2.0	0.645	0.752
≥ 11	13 (61.9)	21 (60.0)	0.091	0.815
< 11	8 (38.1)	14 (40.0)		
HGS, kg[c]	28.0 (18.5–35.0)	35.1 (19.2–36.0)	0.262	0.523
5-CST, sec[c]	9.9 (8.2–11.0)	10.7 (8.9–11.8)	1.023	0.598
SMI, kg/m^2 [a]	6.6 ± 0.9	8.1 ± 1.0	5.097	< 0.001***
IPAQ, kcal/wk[b,c]	450.0 (231.0–693.0)	462.0 (173.2–751.0)	0.097	0.879
< 600	8 (38.1)	15 (42.9)	0.123	0.726
≥ 600	13 (61.9)	20 (57.1)		
LMR[a]	3.4 ± 1.5	3.3 ± 1.7	−0.165	0.692
NLR[c]	5.4 (1.2–6.4)	2.8 (2.4–4.7)	−1.852	0.211
SII[c]	567 (400.0–722.9)	628 (435.7–887.3)	1.133	0.879
Treatment type[b]				
OP	5 (23.8)	9 (25.7)	0.034	0.983
OP+Chemo	7 (33.3)	11 (31.4)		
OP+CRT	9 (42.9)	15 (42.9)		

5-CST, five-time chair stand test; BMI, body mass index; CCI, Charlson Comorbidity Index; Chemo, chemotherapy; CRT, chemoradiotherapy; HGS, handgrip strength; IPAQ, the International Physical Activity Questionnaire; LMR, lymphocyte-to-monocyte ratio; NLR, neutrophil-to-lymphocyte ratio; OP, operation; SII, systemic immune-inflammation index; SMI, skeletal muscle index.

*** $P < 0.001$.

[a] Mean ± standard deviation, Student's t test.

[b] n (%), chi–square test.

[c] Median [interquartile range], nonparametric Mann–Whitney test.

Table 2
Results of the generalized estimating equations analysis for the outcomes.

Variables	Beta	SE	95% CI		Wald χ^2	*P* value
			Lower	Upper		
HGS						
Intercept	27.75	0.55	26.68	28.86	2.98	< 0.001***
Group (sarcopenia)[a]	−1.05	1.02	−3.06	0.96	1.04	0.307
Time						
T_2–T_1	−0.35	0.18	−0.70	0.00	3.80	0.051
T_3–T_1	−0.41	0.24	−0.89	0.06	2.89	0.089
Group × time						
T_2–T_1	0.10	0.27	−0.43	0.63	0.13	0.712
T_3–T_1	0.01	0.38	−0.73	0.76	0.00	0.96
5-CST						
Intercept	8.30	0.30	7.69	8.90	72.36	< 0.001***
Group (sarcopenia)[a]	−0.11	0.52	−1.14	0.91	0.04	0.831
Time						
T_2–T_1	0.20	0.13	−0.04	0.46	2.51	0.113
T_3–T_1	0.20	0.11	−0.02	0.43	3.14	0.076
Group × time						
T_2–T_1	0.51	0.38	−0.24	1.28	1.78	0.182
T_3–T_1	0.15	0.22	−0.28	0.60	0.47	0.493
SMI						
Intercept	7.97	0.17	7.63	8.31	2078.00	< 0.001***
Group (sarcopenia)[a]	−1.64	0.23	−2.10	−1.17	48.07	< 0.001***
Time						
T_2–T_1	−0.44	0.20	−0.85	−0.03	4.59	0.032*
T_3–T_1	−0.27	0.69	−1.41	0.82	2.29	0.720
Group × time						
T_2–T_1	0.07	0.27	−0.47	0.62	0.06	0.793
T_3–T_1	0.48	0.33	−0.17	1.15	2.09	0.148
IPAQ						
Intercept	303.85	86.16	198.89	520.67	23.95	< 0.001***
Group (sarcopenia)[a]	3.77	190.52	−369.6	377.20	0.08	0.908
Time						
T_2–T_1	−110.40	162.46	−288.82	−148.02	10.39	< 0.001***
T_3–T_1	30.09	45.68	−100.89	201.07	0.59	0.594
Group × time						
T_2–T_1	7.23	115.65	−219.43	253.87	0.25	0.617
T_3–T_1	13.57	122.60	−226.72	253.87	0.40	0.912
Albumin						
Intercept	3.67	0.08	3.50	3.83	4.65	< 0.001***
Group (sarcopenia)[a]	0.14	0.20	−0.25	0.54	0.51	0.471
Time						
T_2–T_1	0.03	0.10	−0.16	0.23	0.13	0.716
T_3–T_1	−0.17	0.17	−0.52	0.18	0.90	0.341
Group × time						
T_2–T_1	−0.45	0.27	−1.19	0.12	0.74	0.524
T_3–T_1	−0.23	0.47	−1.16	0.69	0.24	0.624
LMR						
Intercept	3.43	0.34	2.75	4.10	98.63	< 0.001***
Group (sarcopenia)[a]	−0.07	0.57	−1.19	1.04	0.01	0.897
Time						
T_2–T_1	−0.80	0.53	−1.84	0.22	2.33	0.127
T_3–T_1	0.46	0.77	−1.04	1.97	0.36	0.548
Group × time						
T_2–T_1	0.06	0.90	−1.72	1.84	0.00	0.947
T_3–T_1	−1.10	1.06	−3.20	0.98	1.07	0.300
NLR						
Intercept	3.80	0.33	3.14	4.45	1.89	< 0.001***
Group (sarcopenia)[a]	−0.50	0.65	−1.78	0.78	0.58	0.443
Time						
T_2–T_1	1.15	0.24	1.52	3.49	9.94	< 0.001***
T_3–T_1	0.04	0.08	−0.12	0.21	0.23	0.630
Group × time						
T_2–T_1	−0.37	0.37	−1.18	0.36	0.99	0.320
T_3–T_1	0.30	0.18	−0.06	0.67	2.68	0.102
SII						
Intercept	1167.78	130.95	911.12	1424.45	79.52	< 0.001***
Group (sarcopenia)[a]	−405.35	208.03	−813.10	2.39	3.70	0.051
Time						
T_2–T_1	417.70	400.89	−368.02	1203.43	1.08	0.297
T_3–T_1	131.23	531.66	−910.81	1173.28	0.06	0.805

(*continued on next page*)

Table 2 (*continued*)

Variables	Beta	SE	95% CI		Wald χ^2	*P* value
			Lower	Upper		
Group × time						
T_2–T_1	1658.18	1407.81	−1101.09	4417.45	1.38	0.239
T_3–T_1	−265.77	672.22	−1583.32	1051.76	0.15	0.693

T_1, 1 to 3 days before operation (baseline); T_2, 4 to 5 weeks of radiotherapy; T_3, postoperative of 6 months.
*$P < 0.05$; ***$P < 0.001$.
5-CST, five-time chair stand test; CI, confidence interval; HGS, handgrip strength; IPAQ, the International Physical Activity Questionnaire; LMR, lymphocyte-to-monocyte ratio; NLR, neutrophil-to-lymphocyte ratio; SE, standard error; SII, systemic immune-inflammation index; SMI, skeletal muscle index.
[a] Reference: Group (nonsarcopenia).

such as the PA levels, NLR, and SII, the median and interquartile range were used. Categorical variables were expressed as a number and percentage. To compare the baseline characteristics of the 2 groups (with and without sarcopenia), we used nonparametric Mann–Whitney test or Student's t-test for quantitative variables and chi-square test for qualitative variables. GEE models with an exchangeable matrix to assess the changes over time (from T_1 to T_3) and differences between groups for sarcopenia indices, PA levels, and inflammation biomarkers. Logistic regression models were used to evaluate the effects of demographics, clinical characteristics, sarcopenia status, PA levels, and inflammation biomarkers on treatment-related severity of AEs. The receiver operating characteristic (ROC) curve analysis was performed to identify the cutoff values of inflammation biomarkers. Cox proportional hazards model of OS and DFS were used to explore the association between the risk characteristics and survival outcomes of patients. A *P* value < 0.05 was considered statistically significant.

Results

A total of 61 potentially eligible OCC patients met the inclusion criteria, and 56 of them signed the informed consent to participate in this study. In total, 49 patients completed follow-up measures (retention rate of 87.5%). The attrition rates for each time point were 8.9% (T_1 to T_2) and 3.9% (T_2 to T_3), respectively. Fig. 1 presents the details of participant recruitment. The characteristics of the participants presenting sarcopenia were identified using ASWG in 21 (37.5%) patients, and 35 (62.5%) were not. None of our participants had severe sarcopenia. The presence of sarcopenia was associated with a lower SMI score (6.6 ± 0.9 kg/m^2). There were no significant differences in other variables between the groups (Table 1).

Table 2 presents the results of the GEE analysis, which indicates no significant differences in the interaction effects of group and time for all main outcomes. The decline in SMI score was observed between the T_1 and T_2 time points, and there were significant reductions in the sarcopenia group. Compared to T_1, the mean scores for SMI and PA levels decreased significantly at T_2 ($B = -0.44$; 95% confidence interval [CI]: −0.85 to −0.03; $P = 0.032$; $B = -110.40$; 95% CI: −288.82 to −148.02; $P < 0.001$). Additionally, the NLR increased significantly at T_2 ($B = 1.15$; 95% CI: 1.52 to 3.49; $P < 0.001$). Overall, SMI, PA levels, and NLR worsened after postoperative and middle-of-treatment time points (T_2) but remained stable or slightly improved from T_2 to T_3. However, no significant changes were observed in HGS, 5-CST, LMR, and SII scores with respect to time or group effects.

Table 3 presents a list of grade-3 or worse surgical complications and (chemo)radiation-related AEs. Sarcopenic patients had significantly higher incidence rates of grade-3 or worse dysphagia and infection with normal neutrophil counts than nonsarcopenic patients. Importantly, no participant in this study experienced any treatment-related death or had to discontinue radiation therapy because of severe AEs. Detailed information regarding the distribution of pathogens isolated from various bacterial cultures can be found in Appendix A.

Table 4 presents the results of the univariate logistic regression analysis for clinical risk factors associated with the severity of treatment-related AEs. Based on the findings from Table 3, major postoperative complications, and clinical risk factors with an incidence rate of over 40% were included in the predictive model. The ROC curve was constructed for NLR with infection events. A high NLR was defined as > 5, with an area under the curve of 0.68 (Appendix B). In the multivariate analysis, advanced stage (odd ratio [OR] = 3.01, $P = 0.034$) and sarcopenia (OR = 7.62, $P = 0.018$) were associated with dysphagia. Sarcopenia (OR = 3.02, $P = 0.002$) and NLR greater than 5 (OR = 5.38, $P < 0.001$) were associated with infections, as shown in Table 5. The OS and DFS rates for the entire cohort were 85.7% and 72.6%, respectively. Appendix C shows the results of univariate and multivariate Cox proportional hazard regression analyses of OS and DFS. In the univariate analysis, pretreatment low SMI and SMI change were predictors of OS, and only pretreatment low SMI score was a predictor of DFS. In multivariate analysis, pretreatment low SMI score was independently associated with a poor OS (hazard ratio [HR] = 7.00, $P = 0.005$).

Discussion

The present study is the first to assess the changes in various clinical risk factors and their association with treatment-related AEs during the acute phase to recovery outcomes in patients with OCC who underwent primary surgery with (chemo)radiotherapy. The present study analyzed

Table 3
Grade-3 or higher treatment-related adverse events ($N = 56$).

Treatment-related adverse events	Sarcopenia ($n = 21$), *n* (%)	Nonsarcopenia ($n = 35$), *n* (%)	*P* value
Event			
Dindo classification	6 (28.6)	12 (34.3)	0.170
Dysphagia	12 (57.1)	4 (11.4)	< 0.001***
Infection with normal neutrophil	10 (47.6)	6 (17.1)	0.015*
Hematologic event			
Neutrophils	1 (4.8)	2 (5.7)	0.172
Leukocytes	5 (23.8)	6 (17.1)	0.579
Lymphopenia	3 (14.3)	3 (8.6)	0.783
Anemia	9 (42.9)	14 (40.0)	0.784
Neutropenia fever	1 (4.8)	0 (0)	0.987
Platelets	5 (23.8)	5 (14.3)	0.374

*$P < 0.05$; ***$P < 0.001$.

Table 4
Univariable analysis of factors predicting severe adverse events during treatment.

Factors	Dindo classification		Dysphagia		Anemia		Overall infections	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Age (years)								
< 65	1.00		1.00		1.00		1.00	
≥ 65	1.42 (0.36–5.61)	0.609	0.95 (0.26–3.41)	0.945	0.60 (0.19–1.89)	0.388	1.29 (0.40–4.20)	0.666
Alcohol								
Never	1.00		1.00		1.00		1.00	
Former	0.90 (0.13–6.08)	0.914	0.80 (0.11–5.40)	0.819	1.50 (0.26–8.44)	0.646	1.07 (0.08–13.89)	0.958
Current	0.70 (0.15–3.16)	0.643	0.57 (0.14–2.27)	0.431	1.08 (0.30–3.80)	0.901	5.41 (0.92–27.89)	0.053
Smoking								
Never	1.00		1.00		1.00		1.00	
Former	0.26 (0.03–2.11)	0.211	0.50 (0.07–3.31)	0.473	1.92 (0.38–9.60)	0.423	1.95 (0.27–13.98)	0.506
Current	0.53 (0.10–2.61)	0.438	0.91 (0.22–3.82)	0.905	1.95 (0.48–7.84)	0.347	4.20 (0.79–22.35)	0.092
Betel nut								
Never	1.00		1.00		1.00		1.00	
Former	0.08 (0.00–1.04)	0.054	1.08 (0.15–7.64)	0.936	1.50 (0.26–8.44)	0.646	2.50 (0.28–22.04)	0.409
Current	0.30 (0.06–1.58)	0.159	0.94 (0.23–3.85)	0.940	1.08 (0.30–3.80)	0.901	4.73 (0.91–24.49)	0.064
CCI								
< 5	1.00		1.00		1.00		1.00	
≥ 5	1.23 (0.27–5.64)	0.784	1.46 (0.37–5.79)	0.585	3.34 (0.93–11.92)	0.063	1.00 (0.26–3.51)	0.985
Pathologic stage								
I–II	1.00		1.00		1.00		1.00	
III–IV	0.70 (0.17–2.75)	0.609	3.93 (1.29–8.25)	0.027*	1.08 (0.34–3.48)	0.887	1.61 (0.43–5.95)	0.471
BMI, kg/m^2								
< 18.5	0.62 (0.04–1.02)	0.999	0.74 (0.01–1.02)	0.999	4.33 (1.29–9.25)	0.045*	1.54 (0.18–10.64)	0.685
18.5–24.9	1.00		1.00		1.00		1.00	
≥ 25.0	1.16 (0.30–4.42)	0.821	2.30 (0.63–8.32)	0.205	1.37 (0.90–9.25)	0.075	1.76 (1.05–1.92)	0.038*
Sarcopenia								
No	1.00		1.00		1.00		1.00	
Yes	0.19 (0.02–1.78)	0.146	9.44 (2.49–10.82)	0.001**	0.86 (0.25–2.89)	0.811	4.00 (1.14–13.95)	0.030*
Albumin, g/dL								
≥ 3.5	1.00		1.00		1.00		1.00	
< 3.5	1.12 (0.20–6.04)	0.891	3.00 (0.68–13.11)	0.144	4.72 (1.06–12.88)	0.031*	0.66 (0.14–3.02)	0.599
Hb, g/dL								
≥ 11	1.00		1.00		1.00		1.00	
< 11	0.61 (0.15–2.54)	0.504	3.46 (0.93–12.84)	0.063	3.62 (2.17–14.25)	0.024*	1.04 (0.30–3.58)	0.941
IPAQ, kcal/wk								
≥ 600	1.00		1.00		1.00		1.00	
< 600	6.50 (1.17–35.83)	0.032*	1.47 (0.39–5.54)	0.569	1.12 (0.37–3.37)	0.836	1.07 (0.81–1.32)	0.620
LMR[a]	1.01 (0.65–1.58)	0.934	0.76 (0.49–1.19)	0.243	0.53 (0.32–1.84)	0.615	1.12 (0.76–1.63)	0.554
NLR[a]	0.60 (0.13–2.59)	0.494	1.20 (1.13–2.09)	0.041*	1.97 (0.59–6.63)	0.269	7.50 (1.83–11.73)	0.005**
SII[a]	1.00 (0.99–1.00)	0.108	0.99 (0.99–1.00)	0.318	1.00 (0.99–1.00)	0.313	1.00 (0.90–1.01)	0.089

*$P < 0.05$; **$P < 0.01$.
BMI, body mass index; CCI, Charlson Comorbidity Index; CI, confidence interval; Hb, haemoglobin; IPAQ, the International Physical Activity Questionnaire; LMR, lymphocyte-to-monocyte ratio; NLR, neutrophil-to-lymphocyte ratio; OR, odds ratio; SII, systemic-immune inflammation index.
[a] Continues variable.

56 patients with OCC, of whom 37.5% ($n = 21$) had sarcopenia before primary surgery, consistent with previously published prevalence rates.[26] In the follow-up outcomes, data were collected at 3 time points, which included perioperative and (chemo)radiotherapy periods. The results revealed significant changes in SMI and PA levels and NLR from before surgery to the middle of (chemo)radiotherapy. Moreover, during the same period, patients with sarcopenia exhibited a significant decrease in SMI score. Furthermore, sarcopenia and NLR were significantly associated with infections. In addition, sarcopenia and advanced cancer stage were associated with treatment-related dysphagia. Preoperative low SMI was identified as an independent prognostic factor of survival prediction.

Sarcopenia, a condition characterized by the loss of skeletal muscle mass and function, has been identified as a prognostic factor in HNC patients who undergo anticancer therapy and may worsen during treatment.[26] In conformity with prior findings, a scoping review[40] unveiled that patients with HNC frequently encounter a noteworthy reduction in the SMI following surgery and during treatment. After the operation, loss of SMI and PA was accelerated, and the NLR increased. Furthermore, a gradual recovery of these factors was observed about 1.5 months after the completion of radiotherapy. Decline in PA levels in the participants may be a treatment-related symptom or a part of a cluster of inflammation-associated conditions. In a previous prospective descriptive study,[41] daily step count was used as a measure for evaluating PA levels in newly diagnosed HNC patients undergoing curative (chemo)radiotherapy. The study found that in most participants, the nadir in step count was observed during or shortly after treatment, suggesting that changes in PA levels were likely related to treatment. In a previous study involving patients with advanced OCC, the SMI was assessed preradiotherapy, at the third month, and the ninth month after treatment using computed tomography scans.[15] The study showed that patients who experienced muscle loss throughout the 9-month process had a significantly low OS rate (HR = 1.88, $P < 0.001$). However, preradiotherapy sarcopenia was not independently associated with poor survival outcome. In contrast to the previous study[15] that solely encompassed repeated assessments during the radiotherapy course, our present study monitored patients from the preoperative phase until the adjuvant (chemo)radiotherapy completion. Furthermore, our current study cannot predict survival based on the changes in SMI. In our study, the SMI measurements were conducted using bioelectrical impedance analysis, and the definition cutoff value was based on the AWGS guidelines. The measurement period was from preoperative to 6 months postoperatively. Therefore, the discrepancies in measurement methods, SMI baselines, disease severity, and duration of follow-up may have contributed to the inconsistent predictive outcomes of survival. Our findings are consistent with those of previous studies, which revealed that pretreatment SMI independently predicted poor survival

Table 5
Multivariable analysis of factors predicting severe adverse events during treatment.

Factor	Dysphagia		Anemia		Overall infections	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Pathologic stage						
I–II	1.00					
III–IV	3.01 (2.02–7.01)	0.034*				
BMI, kg/m^2						
< 18.5			2.76 (0.82–8.24)	0.899	1.24 (0.70–2.31)	0.567
18.5–24.9			1.00		1.00	
≥ 25.0			1.65 (0.17–10.35)	0.658	1.98 (0.89–1.35)	0.238
Sarcopenia						
No	1.00				1.00	
Yes	7.62 (2.40–9.76)	0.018*			3.02 (1.57–10.62)	0.002**
Albumin, g/dL						
≥ 3.5			1.00			
< 3.5			4.95 (0.85–10.67)	0.167		
Hb, g/dL						
≥ 11			1.00			
< 11			3.60 (0.88–10.72)	0.062		
NLR						
< 5.0					1.00	
≥ 5.0					5.38 (1.72–11.25)	< 0.001***

*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.
BMI, body mass index; CI, confidence interval; Hb, haemoglobin; NLR, neutrophil-to-lymphocyte ratio; OR, odds ratio.

outcomes in patients with OCC.[26] The exact mechanism explaining the association between sarcopenia and adverse survival outcomes is still not fully elucidated. In addition, the optimal treatment strategy for individuals with sarcopenia remains uncertain.[34] Thus, additional research is warranted to investigate the potential causal relationship between sarcopenia and inferior survival outcomes and explore the efficacy of multimodal interventions in preserving muscle mass and function.

Neutrophils display a diverse functional phenotype characterized by the secretion of proinflammatory cytokines, such as interleukin 1, interleukin 6, and tumour necrosis factor. Before and after surgery[42] or (chemo)radiotherapy,[43] elevated NLR is associated with poor clinical outcomes in patients with HNC.[20,44,45] In line with previous studies on sepsis,[46,47] the current study showed that a high NLR is associated with increased risk of infection. Additionally, our findings indicated that patients with sarcopenia are at an increased risk of acquiring infections, consistent with the results of a retrospective population database study.[48] The underlying mechanism by which sarcopenia increases the risk of posttreatment infections is not yet fully understood. However, muscle mass depletion appears to be a risk factor for perioperative infection.[49] Skeletal muscle depletion, combined with an increase in adipose tissues, can trigger the production and release of various proinflammatory cytokines and adipocytokines.[50] Patients with OCC are susceptible to sarcopenia as a result of tumour location and treatment consequences. In addition, sarcopenia resulting from loss of muscle mass and function can exacerbate dysphagia and malnutrition.[51,52] Moreover, during the perioperative period, inflammation and subsequent suppression of the immune system can hinder the functioning of natural killer cells and T lymphocytes.[53] Radiation-induced cell death and inflammation can cause acute AEs in surrounding normal tissues.[54] The reasons can account for the higher incidence of dysphagia with grade 3 or higher in sarcopenic patients with OCC during treatment in the present study. Currently, there are still limitations in effectively addressing malnutrition during treatment. Wang et al.[55] observed no significant impact of nutritional counseling on the weight, body mass index, and body composition of patients with HNC and on radiotherapy in the nutrition intervention arm. However, their study did not record treatment-related AEs that may influence the effectiveness of the strategy for maintaining adequate nutrient intake and achieving well-nourished status.

In our previous retrospective studies,[56,57] we used a regular head and neck computed tomography slice at the level of the third cervical vertebra to measure skeletal muscle mass and to calculate the SMI. Significant association was found between sarcopenia and curative treatment-related toxicities and survival. In the current study, we conducted a prospective investigation in accordance with the guidelines of the AWGS to track muscle mass, muscle strength and physical performance, reaffirming the crucial role of sarcopenia in predicting adverse clinical outcomes in patients with OCC. Although no significant changes were observed in HGS and 5-CST, this lack of significant change could potentially be attributed to physiological and anatomical differences, as well as a tendency for men to exhibit greater strength during assessments, particularly during the initial measurement, which may result in an overestimation of values and subsequent impact on the obtained results.[58] Moreover, other variables, such as age, type of work, ethnicity, and socioeconomic factors, have been observed to influence the HGS and 5-CST values in cancer patients.[59] This study represents a nursing-led effort to demonstrate that treatment-related AEs are significantly elevated in patients suffering from OCC and sarcopenia and undergoing surgery with adjuvant (chemo)radiotherapy. In addition, preoperative low SMI score can predict unfavorable survival outcomes. Hence, we recommend that clinical medical staff (including nurses and doctors) pay close attention to these factors. A multifaceted assessment of sarcopenia, PA levels, and inflammatory markers should be conducted to establish a significant prognostic indicator for treatment outcome in the OCC population.

Limitations

This study has several limitations. Firstly, the sample size was small. Only 56 patients were enrolled from a specific medical cent in eastern Taiwan because of the unique characteristics of the population. Additionally, missing data resulting from patient attrition at each measurement time point may have reduced the statistical power and potentially affected the validity of the study. Nevertheless, the high compliance rate of expected evaluations supports the use of a complete case analysis, which can reduce the variability and amplitude of the reported results. Secondly, the levels of PA were assessed using self-report data, which can introduce bias. Further research is warranted to utilise appropriate PA assessment tools to obtain a more accurate understanding of PA levels in patients undergoing treatment. Third, the area under the ROC curve of the NLR was 0.687, which does not meet the commonly accepted threshold. To overcome this limitation, future studies can consider the use of a multicenter research design with larger sample sizes for a more robust evaluation of the NLR's predictive power. Finally, although side effects were observed during the 6-month period in the longitudinal

study design, these side effects may have had influenced the patients' quality of life. Moreover, the relatively short observation period for survival, coupled with the lack of pathological risk factors, may need to be considered when regarding the predictive power of survival. Therefore, the enrollment period must be extended, and qualitative and quantitative data on treatment outcomes must be collected to provide comprehensive insights into the efficacy and effect of the treatment.

Conclusions

Our study demonstrated significant changes in SMI, PA levels, and NLR during curative treatment of patients with OCC. We found significant associations between sarcopenia and NLR with infections and between sarcopenia and advanced tumor stage with treatment-related dysphagia. Moreover, a preoperative low SMI score was predictive of unfavorable survival outcomes. These findings highlight the importance of the assessment of sarcopenia and NLR levels, which can affect treatment outcomes and patient well-being, in managing OCC patients undergoing surgery and adjuvant therapy.

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CRediT author statement

Chun Hou Huang: Conceptualization, formal analysis, writing original draft preparation, reviewing, editing and supervision. **Tai Chu Peng:** Formal analysis and supervision. **Yu Fu Chou:** Provided patients information and supervision. **Yun Hsin Peng:** Investigation. All authors had full access to all the data in the study, and the corresponding author had final responsibility for the decision to submit for publication. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Declaration of competing interest

All authors have none to declare.

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Ethics statement

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Review Board and Research Ethics Committee of Hualien Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation (IRB No. 109-183-B). All participants provided written informed consent.

Data availability statement

The authors confirm that the data supporting the findings of this study are available within the article and/or its supplementary materials.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.apjon.2023.100261.

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