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ORIGINAL ARTICLE

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Association of low skeletal muscle mass and systemic inflammation with surgical complications and survival after microvascular flap reconstruction in patients with head and neck cancer

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Abstract

Background: Skeletal muscle mass (SMM) and chronic inflammation are associated with postoperative complications and survival.

Methods: Patients with head and neck cancer (HNC) undergoing microvascular free flap reconstruction were included. SMM and neutrophil-to-lymphocyte ratio (NLR) were measured and their association with treatment outcomes analyzed.

Results: Five hundred and fifty-four patients were included. Predictors for complications were elevated NLR in all flaps (OR 1.5), low SMM in radial forearm flap (OR 2.0), and elevated NLR combined with low SMM in fibula flap surgery (OR 4.3). Patients with solely elevated NLR were at risk for flap-related complications (OR 3.0), severe complications (OR 2.2), and when combined with low SMM for increased length of hospital stays (LOS) (+3.9 days). In early-stage HNC, low SMM (HR 2.3), and combined elevated NLR with low SMM (HR 2.6) were prognostics for decreased overall survival.

Conclusions: SMM and NLR are predictive for poor outcomes in patients with HNC undergoing microvascular reconstruction.

KEYWORDS

inflammation, neutrophil-to-lymphocyte ratio, reconstructive surgery, sarcopenia, skeletal muscle mass

1 | INTRODUCTION

Microvascular tissue transfer is the gold standard for reconstruction of complex head and neck defects after extensive resections for head and neck cancer (HNC) or osteoradionecrosis, or traumas.

Reconstructive flap surgery can lead to improved function and aesthetics but is time-consuming and

associated with significant postoperative morbidity. Survival rate of flaps depends on various factors, among which are age, comorbidities, and many unknown factors.[1–3] Ongoing research is required to identify key predictors for postoperative morbidity, to enable better preoperative risk-analysis for development of more individualized treatment planning aiming at improving treatment outcomes.

Several studies have demonstrated that poor nutritional status and body composition changes are associated with an increased risk of surgical complications.[4,5] Patients with HNC are often seen with inadequate oral intake due to tumor site and treatment-related side effects (e.g., xerostomia, mucositis). This may lead to a decrease of lean body mass of which skeletal muscle mass (SMM) is the largest contributor. The prevalence of low SMM, also referred to as sarcopenia, in patients with HNC is estimated to be approximately 40%.[6] Sarcopenia is associated with aging, but can also be secondary to chronic systemic inflammation, malnutrition, and immobilization, regardless of age. In patients with cancer, a risk factor for sarcopenia inherently present is the malignant tumor itself, which may trigger a chronic systemic inflammatory process in the body as a reaction to the tumor. Loss of SMM in patients with cancer is often accompanied with a gain in fat mass, which leads to "hidden sarcopenia."[7] Body mass index (BMI) is therefore a poor representative of patient's body composition. It is already known that surgically treated patients with elevated BMI tend to have longer operative times and endure more blood loss.[8,9] However, sometimes elevated BMI may have a protective effect also known as the obesity paradox.[10] Hidden sarcopenia might explain why BMI has shown to have no predictive value for surgical complications in patients with HNC who undergo reconstructive surgery.[11,12]

Low SMM has shown to predict surgical complications as well as dose-limiting toxicities and decreased survival.[6,13–16] SMM can be quantified on routinely performed diagnostic imaging using computed tomography (CT) or magnetic resonance imaging (MRI) at the level of the third lumbar vertebrae (L3) or the third cervical vertebrae (C3).[17–19] For patients with head and neck cancer, imaging at the level of C3 is routinely performed in the diagnostic workup and for treatment evaluation.

Recently, we performed a study in patients with HNC undergoing reconstruction by use of free fibular flap (FFF) and found low SMM to be predictive for complications and prognostic for survival.[20] This finding is reinforced by a recently performed study in 168 patients with HNC who underwent free flap reconstruction in which low SMM was a predictor for complications.[21] Another recent study in patients with HNC undergoing free flap reconstruction showed that low SMM was associated with discharge to postacute care facilities (instead of home) indicating that patients with low SMM are less tolerant to reconstructive surgery.[22] Except for the study specific on FFF all these studies only included patients who had preoperative abdominal CT scans for SMM measurement at the level of the third lumbar vertebrae (L3). Although SMM measurements at the level of L3 is common in oncological research,[23] this may lead to an inclusion bias in patients with HNC because only patients with advanced-stage HNC are likely to undergo abdominal imaging as part of screening for distant metastasis with PET-CT.[24]

Another marker receiving increased attention across various cancer types is an elevated neutrophil-to-lymphocyte ratio (NLR), a biomarker for systemic inflammation. An elevated NLR has shown to be prognostic for decreased survival in a variety of cancers such as breast cancer,[25] colorectal cancer,[26] esophageal cancer,[27] and pancreatic cancer.[28] Elevated NLR is also predictive for surgical complications in patients with cancer.[29,30] NLR can be easily quantified by dividing routinely measured neutrophil count by lymphocyte count.

This study aims to investigate the impact of preoperative low SMM and elevated systemic inflammation (elevated NLR-ratio) on postoperative complications, length of hospital stays, and disease-free survival (DFS) and overall survival (OS) in oncological patients undergoing head and neck microvascular free flap reconstruction.

2 | MATERIAL AND METHODS

2.1 | Patients and study design

In a retrospective study, all oncological patients who underwent flap reconstructive surgery at the Department of Oral and Maxillofacial Surgery (OMFS) of Queen Elizabeth Hospital in Birmingham, UK, between January 2007 and January 2020, were included. All clinical and demographic variables were collected by use of electronic medical records. The design of this study was approved by the OMFS department of the Queen Elizabeth Hospital. The requirement of informed consent was waived because of its retrospective design.

2.2 | Skeletal muscle mass

SMM was measured as skeletal muscle area (SMA) on pretreatment imaging of the head and neck at the level of the third cervical vertebrae (C3). The axial slide which showed both transverse processes and the entire vertebral

TABLE 1 Patient characteristics

Characteristics	Category	All patients, $N = 554$ (%)
Sex	Male	329 (59.4)
	Female	225 (40.6)
Age (years)	Median (IQR)	60.5 (51.7–69.4)
Flap used	Radial free forearm flap (RFFF)	266 (48.0)
	Free fibula flap (FFF)	136 (24.5)
	Non-RFF–non-FFF[a]	152 (27.4)
Tumor site	Mandible alveolus	154 (27.8)
	Tongue	149 (26.9)
	Floor of mouth	84 (15.2)
	Maxillary alveolus	73 (13.2)
	Buccal mucosa	53 (9.6)
	Oropharynx	8 (1.4)
	Neck	7 (1.3)
	Skin	7 (1.3)
	Soft palate	6 (1.1)
	Hard palate	3 (0.5)
	Paranasal sinus	4 (0.7)
	Salivary gland	3 (0.5)
	Lip	1 (0.2)
	Hypopharynx	1 (0.2)
	Nose	1 (0.2)
TNM stage (for oncologic SCC patients[b])	I	74 (14.6)
	II	85 (16.8)
	III	56 (11.0)
	IV	292 (57.6)
Adult comorbidity evaluation – 27 score	None	207 (37.4)
	Mild	234 (42.2)
	Moderate	99 (17.9)
	Severe	14 (2.5)
Performance status	ECOG 0	286 (51.6)
	ECOG 1	116 (20.9)
	ECOG ≥2	19 (3.4)
	Unknown	133 (24.0)
Smoking status	Never	222 (40.1)
	Current/former	332 (59.9)
Alcohol consumption	Never	197 (35.6)
	Current/former	357 (64.4)
Body mass index (kg/m^2)	Underweight (≤18.5)	40 (7.2)
	Normal weight (18.5 to <25)	240 (43.3)
	Overweight (25 to <30)	184 (33.2)
	Obese (≥30)	90 (16.2)
Neutrophil-to-lymphocyte ratio	Median (IQR)	3 (2.1–4.5)
	Median (IQR)	42.5 (36.2–48.3)

(Continues)

TABLE 1 (Continued)

Characteristics	Category	All patients, $N = 554$ (%)
Lumbar skeletal muscle mass index (cm^2/m^2)		
Neutrophil-to-lymphocyte ratio >3	No	282 (50.9)
	Yes	272 (49.1)
Low skeletal muscle mass[c]	No	177 (31.9)
	Yes	209 (37.7)
	Unknown	168 (30.3)
Hemoglobin (g/L)	Median (IQR)	136 (123–146)
Creatinine (μmol/L)	Median (IQR)	74 (62–87)
Total protein (g/L)	Median (IQR)	74 (70–77)
Albumin (g/L)	Median (IQR)	45 (42–47)
C-reactive protein (mg/L)	Median (IQR)	5 (2–21)

[a]Other flap used: see Figure 1.
[b]Histology of non-SCC patients were adenoid cystic carcinoma (1.6%), osteosarcoma (1.4%), spindle cell carcinoma (1.1%), adenocarcinoma (0.9%), chondrosarcoma (0.5%), mucoepidermoid carcinoma (0.5%), carcinoma ex inverted papilloma (0.4%), melanoma (0.4%), sarcamatoid sarcoma (0.2%), pleiomorphic sarcoma (0.2%), chrondroblastic sarcoma (0.2%), ameloblastic carcinoma (0.2%), adenosquamous carcinoma (0.2%), metastatic high grade endometrial carcinoma (0.2%), leiomyomsarcoma (0.2%), sarcoma NOS (0.2%), and angiosarcoma (0.2%).
[c]Of the 554 patients, preoperative imaging could not be used of 168 patients (30.3%) due to inability to import the imaging into the muscle segmentation software (slice-O-matic). Only patients with known SMM status were included for logistic regression analysis and survival analysis.

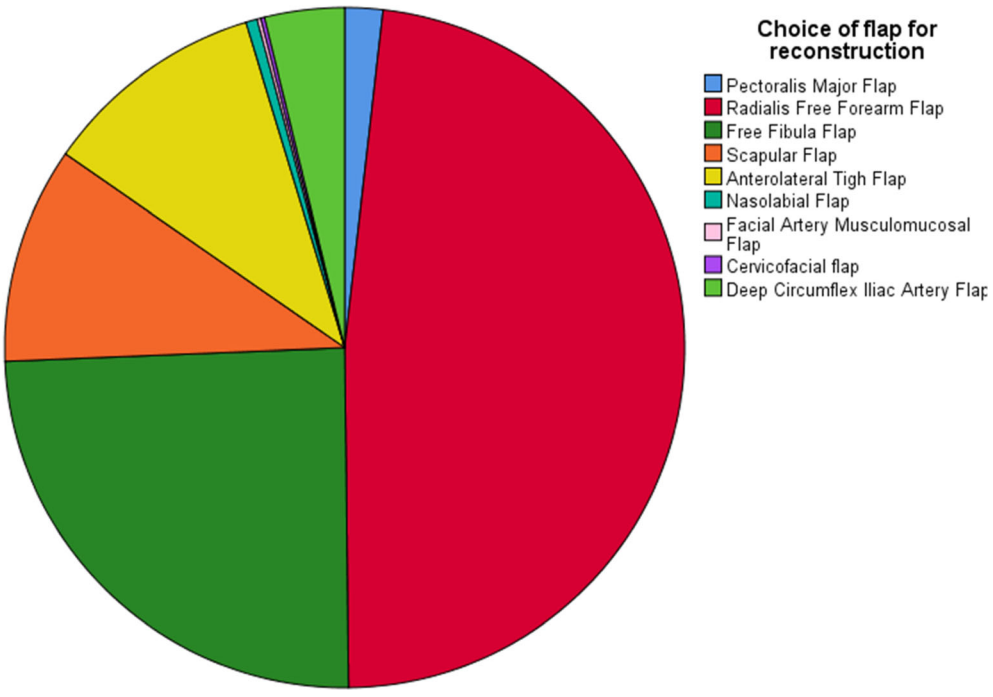

FIGURE 1 Choice of flaps for reconstruction [Color figure can be viewed at wileyonlinelibrary.com]

arc was selected for segmentation of muscle tissue. On CT, muscle area was defined as the pixel area between the muscle-specific radiodensity range of −29 and +150 Hounsfield Units (HU). SMA was calculated as the sum of the delineated areas of the paravertebral muscles and both sternocleidomastoid muscles. Segmentation of muscle tissue was manually performed using the commercially available software package SliceOmatic (Tomovision, Canada) by a single researcher (N.C.). An example of segmentation at the level of C3 is shown in Figure S1, Supporting Information. SMA at the level of C3 was converted to SMA at the level of L3 using a previously published formula as shown in Equation (1).[17] The lumbar skeletal muscle index (LSMI) was calculated by

correcting SMM at the level of L3 for squared height as shown in Equation (2). Low SMM was defined as a LSMI below 43.2 cm^2/m^2. This cutoff value was determined in a separate cohort of patients with HNC,[13]

TABLE 2 Postoperative complications

	All patients, $N = 554$ (%)	
Type of flap complication		
None	490	88.4
Flap failure	23	4.2
Venous congestion	12	2.2
Dehiscence	11	2.0
Partial flap failure	5	0.9
Thrombosis	3	0.5
Necrosis	4	0.7
Arterial congestion	3	0.5
Partial skin breakdown	3	0.5
Type of non-flap complication		
None	343	61.9
Wound infection recipient site	37	6.7
Wound infection donor site	34	6.1
Nerve damage	19	3.4
Wound breakdown	17	3.1
Postoperative bleeding	19	3.4
Dehiscence	9	1.6
Fistula	10	1.8
Pneumonia	13	2.3
Seroma	10	1.8
Hematoma recipient site	6	1.1
Neurological	5	0.9
Plate exposure	5	0.9
Pyrexia e.c.i. treated with antibiotics	4	0.7
Cardiovascular	4	0.7
Chyle leakage	3	0.5
Urinary tract infection	3	0.5
Sialocele	2	0.4
Swelling n.o.s.	2	0.4
Gastrointestinal infection	2	0.4
Pulmonary embolus	1	0.2
Other[a]	6	1.1
Clavien–Dindo grade		
0	295	53.2
I	12	2.2
II	141	25.5
IIIa	12	2.2
IIIb	81	14.6
IVa	7	1.3
IVb	1	0.2
V	5	0.9

[a]Other complications: prolonged respiratory wean due to hypodynamic diaphragm, malocclusion due to flap/plate, hypernatremia which prompted ITU admission, elevated liver function tests e.c.i., fractured clavicle.

$$\begin{aligned}&\mathcal{CSA}\ at\ \mathcal{L}\ni(cm^{\in})=\in\imath\ni\prime\triangle+\infty.\ni\not\ni^{*}\mathcal{CSA}\ at\ \mathcal{C}\ni(cm^{\in})\\&\quad-\prime.\not\propto^{*}\mathcal{A}\}\rceil(\dagger\rceil\dashv\nabla\int)+\prime.\not\triangleq\prime^{*}weight(kg)\\&\quad+\in,\not\triangle\triangle\in^{*}sex(sex=\infty\ for\ female\ and\in for\ male),\end{aligned}\tag{1}$$

$$\mathcal{L}\sqcap\Updownarrow\lfloor\dashv\nabla\ \mathcal{SMI}\ (cm^{\in}/m^{\in})=\mathcal{CSA}\ at\ \mathcal{L}\ni/length\ (m^{\in}).\tag{2}$$

2.3 | Systemic inflammation

NLR was used to evaluate systemic inflammation. According to literature, an NLR >3 indicates high grade of systemic inflammation.[31]

2.4 | Outcome variables

Postoperative complications were defined as any adverse development after surgery. Severity of all complications were scored by use of the Clavien–Dindo classification of surgical complications.[32] Complications were also scored by distinction of flap-related complications and non-flap-related complications. Flap-related complications were defined as all complications concerning the flap. Patients with multiple complications were scored according to their highest grade of complication.

Length of hospital stay (LOS) was defined as the time between date of operation and date of hospital discharge. Disease-free survival (DFS) was defined as the time between diagnosis date and recurrence date or last follow-up, whichever occurred first. Overall survival (OS) was defined as the time between diagnosis date and date of death or last follow-up, whichever occurred first.

2.5 | Statistical analysis

Data analyses were performed using IBM SPSS statistics 25. Descriptive statistics for continuous variables with a normal distribution were presented as mean with standard deviation (SD). Variables with a skewed distribution were presented as median with interquartile range

TABLE 3 Univariate and multivariate analysis for any surgical complications

	Univariate analysis			Multivariate analysis		
Variable	**OR**	**95%CI**	***p*-value**	**OR**	**95%CI**	***p*-value**
All oncological patients with known SMM status (number of patients = 387)						
Sex						
Female	Ref.					
Male	1.2	0.8–1.8	0.4			
Age (years)	1	1.0–1.0	0.3			
Flap used						
Radial forearm	Ref.					
Fibula	0.9	0.5–1.5	0.7			
Others	0.7	0.5–1.2	0.2			
ACE-27						
None	Ref.			Ref.		
Mild	1.1	0.7–1.7	0.8	0.4	0.1–1.6	0.2
Moderate	1.4	0.8–2.4	0.3	0.5	0.1–1.7	0.2
Severe	2.2	0.6–8.0	0.2	0.6	0.1–2.2	0.4
BMI (kg/m^2)						
Normal (18.5–24.9)	Ref.			Ref.		
Underweight (≤18.5)	0.7	0.3–1.5	0.3	0.6	0.2–1.3	0.2
Overweight (25–29.9)	0.9	0.6–1.5	0.8	0.9	0.6–1.5	0.7
Obese (≥30)	1.1	0.6–2.0	0.7	1.1	0.6–2.0	0.8
Smoking status[a]						
Never	Ref.					
Current/former	0.9	0.6–1.3	0.5			
Alcohol use[a]						
Never	Ref.					
Current/former	1	0.7–1.5	0.9			
Low hemoglobin, ≤100 g/L						
No	Ref.					
Yes	2	0.8–4.8	0.2			
Elevated NLR, >3						
No	Ref.			Ref.		
Yes	1.6	1.1–2.3	**0.045**	1.5	1.01–2.3	**0.04**
Low albumin, ≤40 g/L						
No	Ref.					
Yes	1.1	0.6–2.0	0.7			
Low SMM[b]						
No	Ref.					
Yes	0.9	0.6–1.3	0.5			
SMM and NLR						
Normal SMM and NLR	Ref.					
Normal NLR, low SMM	1	0.6–1.8	1			
Normal SMM, NLR >3	1.8	1.0–3.2	*0.05*			
Low SMM and NLR >3	1.3	0.8–2.3	0.3			

TABLE 3 (Continued)

	Univariate analysis			Multivariate analysis		
Variable	**OR**	**95%CI**	***p*-value**	**OR**	**95%CI**	***p*-value**
Oncological patients treated with a radial forearm free flap (number of patients = 193)						
Sex						
Female	Ref.					
Male	1.8	1.0–3.2	0.05			
Age (years)	1	1.0–1.0	0.8			
ACE-27 score						
None	Ref.					
Mild	0.9	0.5–1.7	0.7			
Moderate	0.9	0.4–2.0	0.8			
Severe						
BMI (kg/m^2)						
Normal (18.5–24.9)	Ref.			Ref.		
Underweight (≤18.5)	0.5	0.2–1.8	0.3	0.6	0.2–2.0	0.4
Overweight (25–29.9)	1	0.5–1.9	0.9	0.8	0.4–1.5	0.5
Obese (≥30)	1	0.4–2.3	1	0.7	0.3–1.8	0.5
Smoking status						
Never	Ref.					
Current/former	0.8	0.5–1.5	0.5			
Alcohol use						
Never	Ref.					
Current/former	0.9	0.5–1.6	0.7			
Low hemoglobin, ≤100 g/L						
No	Ref.					
Yes	0.5	0.05–5.7	0.6			
Elevated NLR, >3						
No	Ref.					
Yes	1.3	0.7–2.3	0.4			
Low albumin, ≤40 g/L						
No	Ref.					
Yes	0.8	0.3–2.2	0.6			
Low SMM[b]						
No	Ref.			Ref.		
Yes	1.9	1.1–3.4	**0.03**	2	1.1–3.8	**0.03**
SMM and NLR						
Normal SMM and NLR	Ref.					
Normal NLR, low SMM	1.8	0.9–3.3	*0.08*			
Normal SMM, NLR >3	1.4	0.6–3.2	0.4			
Low SMM and NLR >3	1.3	0.7–2.5	0.5			
Oncological patients treated with a fibula flap (number of patients = 88)						
Sex						
Female	Ref.					
Male	0.9	0.4–2.0	0.7			

(Continues)

TABLE 3 (Continued)

	Univariate analysis			Multivariate analysis		
Variable	**OR**	**95%CI**	***p*-value**	**OR**	**95%CI**	***p*-value**
Age (years)	1	1.0–1.1	0.3			
ACE-27						
None	Ref.			Ref.		
Mild	1.5	0.6–3.8	0.4	1.5	0.5–3.9	0.4
Moderate	1.4	0.4–5.3	0.6	1.6	0.4–6.5	0.5
Severe	1.4	0.1–24.7	0.8	1.3	0.1–25.1	0.9
BMI (kg/m^2)						
Normal (18.5–24.9)	Ref.					
Underweight (≤18.5)	3.7	0.4–38.3	0.3			
Overweight (25–29.9)	1.1	0.4–2.7	0.9			
Obese (≥30)	0.9	0.2–3.2	0.8			
Smoking status						
Never	Ref.					
Current/former	0.9	0.4–2.1	0.9			
Alcohol use						
Never	Ref.					
Current/former	1.3	0.6–3.0	0.5			
Low hemoglobin, ≤100 g/L						
No	Ref.					
Yes						
Elevated NLR, >3						
No	Ref.					
Yes	3.3	1.3–8.0	**0.009**			
Low albumin, ≤40 g/L						
No	Ref.					
Yes	2.2	0.7–6.7	0.2			
Low SMM[b]						
No	Ref.					
Yes	1.7	0.7–3.9	0.3			
SMM and NLR						
Normal SMM and NLR	Ref.			Ref.		
Normal NLR, low SMM	1.5	0.4–5.7	0.6	1.7	0.4–6.8	0.5
Normal SMM, NLR >3	3.4	0.9–13.4	0.08	3.5	0.9–13.7	0.07
Low SMM and NLR >3	4.1	1.3–13.2	**0.02**	4.3	1.3–14.2	**0.02**
Oncological patients treated with non-radialis, non-fibula flap (number of patients = 106)						
Sex						
Female	Ref.					
Male	0.8	0.4–1.7	0.5			
Age (years)	1	1.0–1.1	0.3			
ACE-27						
None	Ref.			Ref.		
Mild	1.3	0.5–3.3	0.6	1.3	0.5–3.4	0.6

TABLE 3 (Continued)

	Univariate analysis			Multivariate analysis		
Variable	**OR**	**95%CI**	***p*-value**	**OR**	**95%CI**	***p*-value**
Moderate	3	1.0–9.5	0.06	2.6	0.8–8.6	0.1
Severe	1.3	0.2–9.2	0.8	1.2	0.2–8.7	0.9
BMI (kg/m^2)						
Normal (18.5–24.9)	Ref.					
Underweight (≤18.5)	0.5	0.1–2.0	0.3			
Overweight (25–29.9)	0.7	0.3–1.8	0.5			
Obese (≥30)	1.7	0.5–5.7	0.4			
Smoking status						
Never	Ref.					
Current/former	1	0.5–2.2	1			
Alcohol use						
Never	Ref.					
Current/former	0.9	0.4–1.9	0.7			
Low hemoglobin, ≤100 g/L						
No	Ref.					
Yes	1.8	0.6–5.7	0.3			
Elevated NLR, >3						
No	Ref.					
Yes	1.2	0.5–2.6	0.7			
Low albumin, ≤40 g/L						
No	Ref.					
Yes	1.1	0.4–2.8	0.8			
Low SMM[b]						
No	Ref.					
Yes	1.4	0.6–3.0	0.5			
SMM and NLR						
Normal SMM and NLR	Ref.			Ref.		
Normal NLR, low SMM	2.7	0.8–9.2	0.1	2.1	0.6–7.7	0.2
Normal SMM, NLR >3	2.3	0.7–7.7	0.2	2	0.6–7.0	0.3
Low SMM and NLR >3	1.9	0.6–6.0	0.3	1.6	0.5–5.2	0.5

Note: The statistically significant values are marked in bold; the trend for significance values are marked in italics.

Abbreviations: ACE-27, adult comorbidity evaluation-27; BMI, body mass index; NLR, neutrophil-lymphocyte ratio; SMM, skeletal muscle mass.

[a]Due to unknown alcohol and smoking status of 40 patients, imputation analysis was performed.

[b]Low SMM defined as LSMI ≤43.2 cm/m^2.

(IQR). Categorical variables were presented as frequencies and percentages. Logistic regression was used for univariate and multivariate analysis of surgical complications; only patients with known SMM status were included for analysis. Cox proportional hazard regression model was used for univariate and multivariate analysis of survival, only patients with known SMM status were included for analysis. Covariates used in the multivariate analysis were selected based on clinical significance or selected based on statistical significance ($p < .05$) in univariate analysis. Correlation analysis was performed by use of Pearson's correlation analysis for variables with a normal distribution and Spearman's correlation analysis was used for non-normally distributed variables. In case of high multicollinearity of variables in the multivariate analysis, highly correlated predictors were not included to prevent biased estimation.[33] Statistical significance was evaluated at the 0.05 level using two-sided tests. Survival was visualized using Kaplan–Meier survival curves.

TABLE 4 Univariate and multivariate cox proportional hazards model for prognostic factors for OS and DFS in early and advanced stage HNSCC

	Univariate analysis			Multivariate analysis 1			Multivariate analysis 2		
Variable	**HR**	**95%CI**	***p*-value**	**HR**	**95%CI**	***p*-value**	**HR**	**95%CI**	***p*-value**
Oncological HNSCC patients: TNM stage I-II – OS									
Sex									
Female	Ref.								
Male	0.5	0.3–0.9	**0.01**						
Age (years)	1.1	1.04–1.1	**0.0001**						
ACE-27 score									
None	Ref.			Ref.			Ref.		
Mild	1.6	0.8–2.9	0.2	1.6	0.9–3.0	0.1	1.5	0.8–2.9	0.2
Moderate	1.8	0.8–4.2	0.2	1.5	0.7–3.6	0.3	1.7	0.7–4.0	0.2
Severe	1.9	0.4–8.2	0.4	2.2	0.5–9.5	0.3	2.6	0.6–11.5	0.2
BMI (kg/m^2)	0.95	0.9–1.0	0.1						
Hemoglobin	0.99	0.97–1.0	0.2						
Hemoglobin ≤100									
No	Ref.								
Yes	1.8	0.2–13.2	0.6						
NLR									
≤3.0	Ref.								
>3.0	1.3	0.7–2.2	0.4						
Low SMM									
No	Ref.			Ref.					
Yes	2.3	1.2–4.4	**0.01**	2.3	1.2–4.4	**0.01**			
SMM and NLR									
Normal SMM and NLR	Ref.						Ref.		
Normal NLR, low SMM	1.6	0.7–2.6	0.3				1.5	0.7–3.5	0.3
Normal SMM, NLR >3	0.7	0.2–2.3	0.5				0.6	0.2–2.1	0.4
Low SMM and NLR >3	2.7	1.2–6.3	0.02				2.6	1.1–6.0	**0.03**
Oncological HNSCC patients: TNM stage III-IV – OS									
Sex									
Female	Ref.								
Male	1.3	0.9–1.9	0.2						
Age (years)	1	1.0–1.0	0.7						
ACE-27									
None	Ref.								
Mild	1.6	0.8–2.9	0.2						
Moderate	1.8	0.8–4.2	0.2						
Severe	1.9	0.4–8.2	0.4						
BMI (kg/m^2)	0.94	0.90–0.98	**0.004**	0.96	0.93–0.99	**0.01**	0.94	0.9–0.98	**0.008**
Hemoglobin	0.99	0.98–0.99	0.02				0.99	0.98–0.99	**0.03**
Hemoglobin ≤100									
No	Ref.								
Yes	1.5	0.8–2.6	0.2						

TABLE 4 (Continued)

	Univariate analysis			Multivariate analysis 1			Multivariate analysis 2		
Variable	**HR**	**95%CI**	***p*-value**	**HR**	**95%CI**	***p*-value**	**HR**	**95%CI**	***p*-value**
NLR									
≤3.0	Ref.			Ref.					
>3.0	1.2	0.8–2.2	0.4	1.3	0.9–1.7	0.1			
Low SMM									
No	Ref.								
Yes	1.3	0.9–1.8	0.2						
SMM and NLR									
Normal SMM and NLR	Ref.								
Normal NLR, low SMM	1.4	0.8–2.4	0.2						
Normal SMM, NLR >3	1.3	0.8–2.2	0.3						
Low SMM and NLR >3	1.5	0.9–2.5	*0.09*						
Oncological HNSCC patients: TNM stage I-II – DFS									
Sex									
Female	Ref.						Ref.		
Male	0.4	0.2–0.8	**0.02**				0.5	0.2–1.0	0.06
Age (years)	1.1	1.01–1.1	**0.001**				1.04	1.01–1.08	**0.007**
ACE-27									
None	Ref.			Ref.			Ref.		
Mild	0.8	0.4–1.9	0.7	0.9	0.4–1.9	0.7	0.9	0.4–2.0	0.8
Moderate	2.2	0.9–5.5	0.09	1.9	0.8–4.8	0.2	2.2	0.9–5.6	*0.09*
Severe	1.3	0.2–9.7	0.8	1.4	0.2–10.7	0.7	1	0.1–7.8	0.99
BMI (kg/m^2)	0.95	0.9–1.0	0.2						
Hemoglobin	0.99	0.9–1.0	0.4						
Hemoglobin ≤100									
No	Ref								
Yes	0.05	0–∝	0.7						
NLR									
≤3.0	Ref.								
>3.0	1.2	0.6–2.4	0.6						
Low SMM									
No	Ref.			Ref.					
Yes	2.2	1.0–5.0	*0.05*	2	0.9–4.6	*0.09*			
SMM and NLR									
Normal SMM and NLR	Ref.								
Normal NLR, low SMM	3.4	1.0–11.8	*0.06*						
Normal SMM, NLR >3	2.2	0.5–9.1	0.3						
Low SMM and NLR >3	3.3	0.9–12.1	*0.07*						
Oncological HNSCC patients: TNM stage III-IV – DFS									
Sex									
Female	Ref.								
Male	1	0.7–1.5	0.9						
Age (years)	0.98	0.97–1.0	0.05	0.98	0.96–0.99	0.03	0.98	0.96–0.99	**0.02**

(Continues)

TABLE 4 (Continued)

	Univariate analysis			Multivariate analysis 1			Multivariate analysis 2		
Variable	**HR**	**95%CI**	***p*-value**	**HR**	**95%CI**	***p*-value**	**HR**	**95%CI**	***p*-value**
ACE-27									
None	Ref.								
Mild	0.8	0.5–1.2	0.2						
Moderate	1	0.6–1.8	1						
Severe	0.3	0.04–2.0	0.2						
BMI (kg/m^2)	0.9	0.9–1.0	0.2						
Hemoglobin	0.9	0.9–1.0	0.1	0.99	0.98–1.0	0.07			
Hemoglobin ≤100									
No	Ref.						Ref.		
Yes	1.5	0.8–2.9	0.3				1.4	0.7–2.9	0.4
NLR									
≤3.0	Ref.								
>3.0	1.1	0.7–1.7	0.5						
Low SMM									
No	Ref.								
Yes	1.3	0.8–2.0	0.2						
SMM and NLR									
Normal SMM and NLR	Ref.						Ref.		
Normal NLR, low SMM	1.1	0.6–2.1	0.8				1.3	0.7–2.4	0.5
Normal SMM, NLR >3	1	0.5–1.8	0.9				1	0.5–1.9	0.9
Low SMM and NLR >3	1.4	0.8–2.4	0.3				1.6	0.9–2.8	0.1

Note: The statistically significant values are marked in bold; the trend for significance values are marked in italics.
Abbreviations: ACE-27, Adult Comorbidity Evaluation-27; BMI, body mass index; NLR, neutrophil-lymphocyte ratio; SMM, skeletal muscle mass.

3 | RESULTS

3.1 | Patient characteristics

Descriptive data are described in Table 1. In total, 554 oncological patients were included. Median age at diagnosis was 60.5 years (IQR 51.7–69.4). Of these patients, 507 patients (91.5%) were diagnosed with head and neck squamous cell carcinoma (HNSCC). Majority of patients were male (59.4%). Most used flap was the radial forearm free flap (RFFF) ($n = 266$, 48%). Figure 1 shows the flaps used for reconstruction. Table 1 provides information about the included patients.

3.2 | Postoperative complications

Table 2 shows the types of flap and non-flap-related complications. All complications were graded by the Clavien–Dindo grading system. Of the 554 patients, 64 (11.6%) experienced a flap-related complication. Flap failure rate was 4.2%. Non-flap-related complications occurred in 211 patients (38%). Median time between operation date and complication date was 2 weeks (IQR 0.48–4.8 weeks).

Most common non-flap-related complication was a wound infection at the recipient site (6.7%). Most complications (25.5%) were scored as Clavien–Dindo grade 2. Eighty-one patients (14.6%) had a Clavien–Dindo grade 3b complication which meant that the severity of their complication necessitated intervention under general anesthesia.

As shown in Table 3, univariate analysis in oncological patients with surgical complications as dependent variable determined elevated NLR as a significant predictive factor (HR 1.6, 95%CI 1.1–2.3, $p < 0.05$). In multivariate analysis elevated NLR remained a significant predictive factor for surgical complications (OR 1.5, 95%CI 1.01–2.3, $p = 0.04$), independent of patients' comorbidities and BMI. In order to get more insight in the predictive variables for different types of flap reconstructive surgeries, oncological patients were categorized into three subgroups of patients (with available SMM measurement) based on the chosen flap: RFFF, FFF, and other flaps (non-RFFF–non-FFF). This yielded a RFFF subgroup with 193 patients, a FFF group

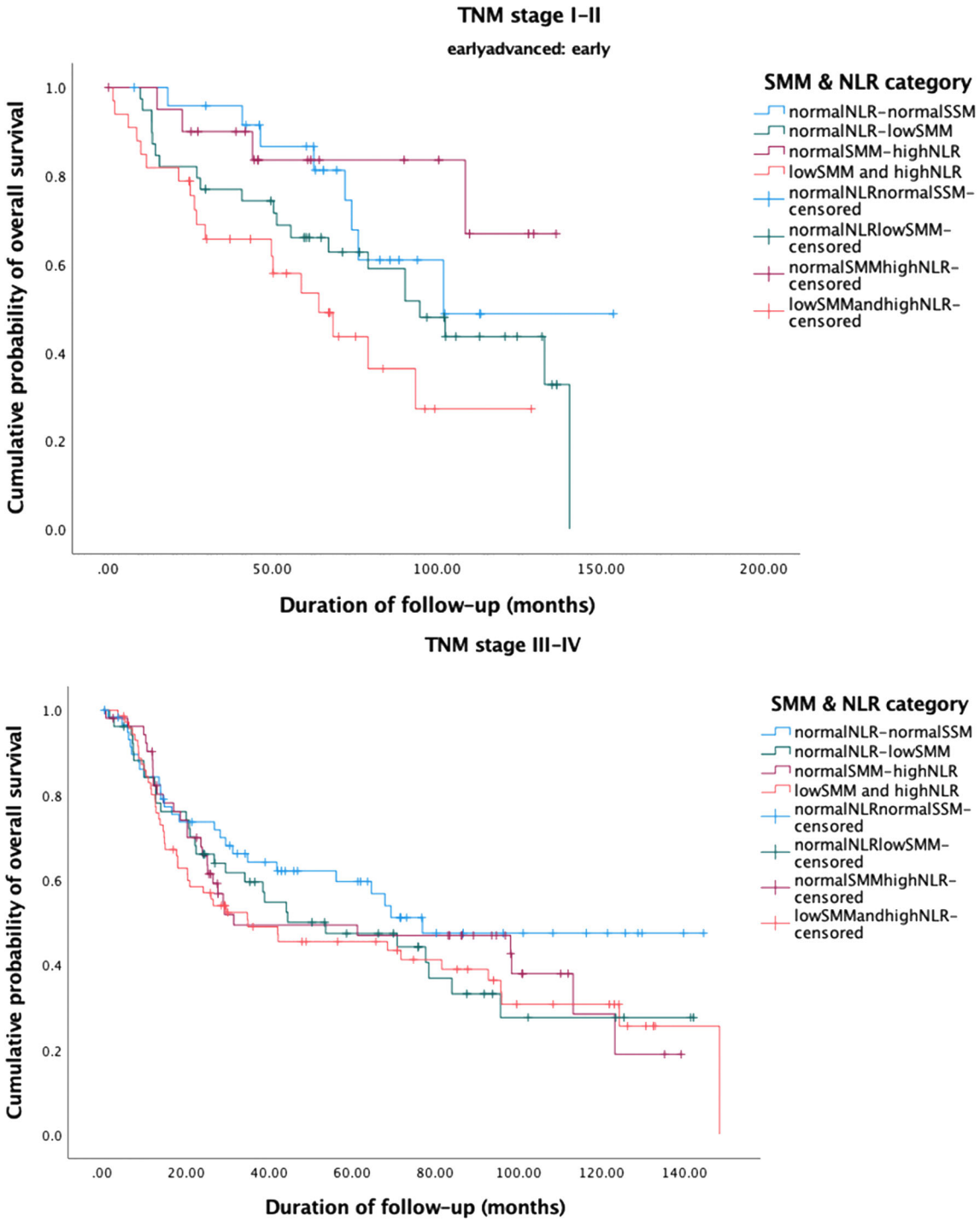

FIGURE 2 Kaplan–Meier survival curves for OS for patients with early stage HNSCC according to SMM and NLR status shows significant differences in overall survival between patients with low SMM compared to patients without low SMM, especially in those patients with combined low SMM and elevated NLR (log rank $\chi^2 = 10.2$, $p = 0.02$). Kaplan–Meier survival curves for overall survival of patients with advanced stage HNSCC according to SMM and NLR status shows no significant differences in survival (log rank $\chi^2 = 3.0$, $p = 0.4$) [Color figure can be viewed at wileyonlinelibrary.com]

with 88 patients and a group of patients with other flaps with 106 patients. Table 3 shows the univariate and multivariate analysis with surgical complications as dependent variable distinguishing predictive factors in the flap-subgroups. For RFFF surgery, multivariate analysis determined low SMM (OR 2.0, 95%CI 1.1–3.8, $p = 0.03$) as a predictor, independent of BMI. Sex was not included in multivariate analysis due to multicollinearity between

SMM and sex ($r^2 = 0.62$, $p < 0.001$). For FFF surgery, multivariate analysis distinguished the combination of elevated NLR with low SMM (OR 4.3, 95%CI 1.3–14.2, $p = 0.02$) as a predictor for surgical complications, independent of patients' comorbidities. For non-RFF–non-FFF-flap surgery, no predictors for complications could be distinguished.

When performing multivariate analysis to distinguish predictors for any flap-related complications, combined elevated NLR with normal SMM was predictive for flap-related complications (OR 3.0, 95%CI 1.2–7.5, $p = 0.02$) independent of hemoglobin levels (OR 1.1, 95%CI 1.0–1.0, $p = 0.3$) and BMI (OR 1.0, 95%CI 0.3–2.8, $p = 0.5$), and for severe complications (Clavien–Dindo grade ≥3b) (OR 2.2, 95%CI 1.1–4.5, $p = 0.04$) independent of hemoglobin levels (OR 1.0, 95%CI 1.0–1.0, $p = 0.04$) and patients' comorbidities (OR mild 1.3, OR moderate 1.1, OR severe 1.4, all $p > 0.05$).

3.3 | Length of hospital stay

Median LOS for all included patients was 13 days with an IQR of 11–18 days. When comparing mean LOS between patients with and without low SMM, patients with low SMM had comparable LOS (16.6 days, SD 10.5) compared to patients without low SMM (15.7 days, SD 17.0 days) (mean difference 0.9 days, 95%CI −1.8 to 3.5, $p = 0.5$). This difference was not statistically significant. Patients with elevated NLR had a significant risk for longer LOS (17.7 days, SD 17.0 days) compared to patients with low NLR (14.5 days, SD 9.2 days) (mean difference 3.2 days, 95%CI 0.5–5.9, $p = 0.02$). Also, patients with elevated NLR and low SMM had a significant longer LOS (17.3 days, SD 10.4) compared to patients without combined elevated NLR and low SMM (13.5 days, SD 7.7) (mean difference 3.9 days, 95%CI 1.4–6.3 days, $p = 0.002$).

3.4 | Survival analysis

Median follow-up time was 39.04 months (IQR 17.1–76.6). At the end of the study, 276 (49.8%) patients had died, and 182 (32.9%) oncological patients had developed a recurrence.

We choose to perform survival analysis for the subgroup of patients with HNSCC ($n = 507$). SMM and NLR status was only available in a subgroup of patients with HNSCC ($n = 352$); therefore, we choose to evaluate the prognostic impact of these variables and other variables in this subgroup. Because TNM stage is a known prognostic factor, we decided to investigate the prognostic impact of low SMM and elevated NLR in patients with early (TNM stage I-II) and advanced stage (TNM stage III-IV) HNSCC. Table 4 shows the univariate and multivariate cox regression analysis of prognostic variables for DFS and OS. For DFS, multivariate analysis determined age to be prognostic in early stage HNSCC (HR 1.04, 95% CI 1.01–1.1, $p < 0.0$) and in advanced stage HNSCC (HR 0.98, 95%CI 0.96–0.99, $p = 0.02$). For OS, in patients with early stage HNSCC, multivariate analysis showed low SMM (HR 2.3, 95%CI 1.2–4.4, $p = 0.01$) and combined elevated NLR with low SMM (HR 2.6, 95%CI 1.1–6.0, $p = 0.03$) to be significant prognostics for decreased OS, independent of comorbidity. Age and sex were not included in multivariate analysis due to multicollinearity between SMM and age ($r^2 = -0.4$, $p < 0.001$) and SMM and sex ($r^2 = 0.62$, $p < 0.001$). For OS, in patients with advanced stage HNSCC, in multivariate analysis only BMI (HR 0.9, 95%CI 0.9–0.98, $p < 0.001$) and hemoglobin (HR 0.99, 95%CI 0.98–0.99, $p = 0.03$) were prognostic for decreased OS.

Figure 2 shows the Kaplan–Meier overall survival curves for patients with early and advanced stage HNSCC according to SMM and NLR status. Patients with combined elevated NLR and low SMM were at significant risk for decreased OS in early stage HNSCC (log rank $\chi^2 = 10.2$, $p = 0.02$).

4 | DISCUSSION

This study showed that low SMM and elevated NLR have significant predictive impact for postoperative complications and LOS and prognostic impact for survival in (subgroups of) patients undergoing microvascular free flap head and neck reconstruction.

The prevalence of low SMM and high NLR found in patients with HNSCC was 57.0% and 48.3%, respectively. A previous meta-analysis in 2483 patients with HNC found a similar prevalence of low SMM (39.4%).[6] Low SMM is also prevalent in patients with non-HNC. A previous study performed in colorectal cancer with 2470 patients also found a similar prevalence of low SMM (44%) and elevated NLR (46%). A significant prognostic value of these markers for decreased overall survival was also found.[34]

SMM and inflammation have been associated with increased risk of postoperative complications and mortality in various types of cancer such as lung cancer, gastrointestinal cancer, pancreatic cancer, hepatobiliary cancer, breast cancer, and cancers of the reproductive system.[35–40] Virchow was the first to provide a possible link between inflammation and cancer by observing the presence of leukocytes within tumors in the 19th century. Since then, various studies published about the

significant role of inflammation in cancer and only during the last decade clear evidence has been obtained to show the critical role of inflammation in tumorigenesis.[41] It is also known that local inflammation in the microenvironment of the tumor leads to chronic systemic inflammation with significant effects on patient's body weight and amount of lean tissue of which SMM is the largest contributor, also known as cancer cachexia.[42] Also, neutrophils and lymphocytes are host inflammation markers which provide angiogenic, epithelial and stromal growth factors that may cause tumor progression.[43] The role of patients' grade of systemic inflammation in surgically treated patients has been increasingly recognized over the past decade.[40,44–49]

Muscle mass and inflammation also gained increased attention in the field of medical oncology, especially in patients with HNC. Low SMM has shown to be predictive for chemotherapy dose-limiting toxicities,[13] radiotherapy toxicities, increased risk of pharyngocutaneous fistulas in patients undergoing total laryngeal extirpation,[50] decreased survival in patients with oral cavity cancers,[51] and increased risk of FFF failure and other surgical complications in oral cancer patients.[20] Low SMM has also shown to be prognostic for decreased OS and DFS in patients with head and neck cancer.[6] Our previous finding showed that low SMM is a significant predictor of surgical complications and prognostic for OS in patients with oral cancer undergoing FFF surgery, in this cohort we confirm this and found that the combination of low SMM with elevated NLR (OR 4.3, $p < 0.05$) was predictive for surgical complications. Due to the low flap failure rate, especially in patients with FFF surgery ($n = 7$), it was not possible to specifically evaluate the impact of low SM on failure rate; however, we assume that the dire effects of low SMM on physical recovery also applies to this flap and that low SMM is a predictive factor for failure rate, as found in our previous study cohort.[20]

Prognostic impact of SMM and NLR was only seen in patients with early stage HNSCC. It is possible that advanced stage HNSCC has already such a poor prognosis that no prognostic impact was seen for SMM and NLR. For advanced stage HNSCC, hemoglobin had significant (but low) prognostic impact for OS. This finding is in accordance with previous literature, which shows that the relative risk of death increased by 75% in anemic patients with head and neck cancer.[52] Also in patients who underwent surgery and adjuvant radiotherapy for locally advanced HNSCC, low hemoglobin appears to be an important prognostic factor.[53]

In this cohort, we found a significant predictive and prognostic impact of elevated NLR. Previous research also shows the prognostic impact of elevated NLR for decreased survival in patients with HNC.[54] To date, only few articles describe the impact of elevated NLR in surgically treated patients with HNC. Kuzucu et al. conducted a study in 145 patients undergoing parotidectomy and 83 healthy persons and found that elevated NLR was significantly higher in patients undergoing surgery for malignant parotid mass.[55] This supports the link between inflammation and cancer. Son et al. performed a retrospective study in 369 patients and found that elevated NLR was significantly associated with increased risk of surgical site infection in patients with HNC undergoing major oncologic resection.[56] The present study supports this finding. NLR is not only an index of inflammation, but is also known to reflect nutritional status, as the total lymphocyte count is decreased in cases of malnutrition.[57] The exact underlying mechanism of how low SMM and elevated NLR attributes to surgical complications is not yet elucidated. Inflammation may underline muscle wasting and may also be reinforced by it. Inflammatory mediators promote catabolic metabolism which leads to increased protein degradation and decreased regeneration. Low SMM and high NLR may therefore also interfere with wound healing.

Our study has some limitations. Due to the retrospective design of the study, information was not completely available regarding ischemic time, intraoperative hypotension, operative time, and anticoagulant administration. These factors are known to (potentially) have an impact on surgical complications. Besides this limitation, our study has also some strengths. First, we included a large sample size with detailed socio-demographic and clinical factors. Second, we measured SMM at the level of C3 instead of L3 which minimizes the risk of only including advanced cases of HNC. Third, this is the first study evaluating the impact of SMM and systemic inflammation in patients undergoing head and neck microvascular reconstruction.

Prevention or treatment of low SMM in head and neck patients remains a challenge due to the high prevalence of malnutrition in these patients. Malnutrition may lead to low SMM and is a potential modifiable factor in the treatment of low SMM; low SMM itself can also result in malnutrition due to dysphagia. Although malnutrition and low skeletal muscle (sarcopenia) considerable overlap in their consequences on treatment outcomes, these are distinct conditions with distinct etiologies and treatment strategies. Whereas treatment of malnutrition is based on restoring nutrition, providing nutrition alone will not restore the quantity of skeletal muscle mass.

It is worthwhile to study if interventions aimed at preservation and/or gain of SMM such as preoperative multimodal rehabilitation programs that include nutritional support, physical therapy and motivational psychotherapy could be effective in preventing adverse

outcomes associated with low SMM and elevated NLR. Pharmacological interventions and supplements targeting SMM might also be promising.[58] For example, omega-3-fatty acids may alter body composition by anti-inflammatory effects and thereby contribute to increased anabolism, improve insulin response and glucose transport and reduce triglyceride accumulation in skeletal muscle.[59] Trials are performed where cachexia in patients with cancer is treated with omega-3 fatty acid supplementation and nonsteroidal anti-inflammatory drugs which underlines the inter-relationship between inflammation and muscle wasting.[60]

5 | CONCLUSIONS

SMM and NLR are easily evaluated, noninvasive biomarkers which are associated with an increased risk of complications, longer LOS, and decreased survival in patients undergoing microvascular free flap reconstruction in the head and neck area.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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