

# Impact of low skeletal muscle mass on postoperative complications in head and neck cancer patients undergoing free flap reconstructive surgery – A systematic review and meta-analysis

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## ABSTRACT

Low skeletal muscle mass is emerging as an adverse predictive and prognostic factor in cancer patients. The use of this parameter as a risk factor for complications after surgery is not currently used in clinical practice. This meta-analysis aims to assess the association of low skeletal muscle mass defined by radiological criteria and complications after reconstructive microsurgery in head and neck cancer patients. A systematic review for articles was performed using the PubMed, EMBASE database and by manual search. Articles that assessed low skeletal muscle mass and its impact on postoperative complications in head and neck cancer patients undergoing free flap surgery were selected. Pooled estimates of postoperative outcome data were calculated by extracting the odds ratio (OR) and 95% confidence interval (CI). The search strategy returned with 6 studies meeting the inclusion criteria. A total of 1082 patients were analyzed. The prevalence of low skeletal muscle mass between studies ranged from 24.6% to 61.5%. The meta-analysis showed an OR for complications after surgery of 2.42 (95% CI 1.53–3.32,  $p = 0.00$ ). The study therefore concludes that skeletal muscle mass is an independent risk factor for postoperative complications in head and neck cancer reconstructive surgery patients. This argues for implementing screening for low skeletal muscle in preoperative management to optimize surgical decision making.

## Introduction

Sarcopenia is characterized by depletion of skeletal muscle mass (SMM) and strength. It is associated with an adverse effect on the prognosis of patients with cancer [1,2]. The European Working Group on Sarcopenia in Older People (EWGSOP) has presented multiple tests and tools for the characterization of sarcopenia in a consensus report [3]. Various methods to determine SMM such as dual-energy X-ray absorptiometry, calculating the cross-sectional muscle area (CSMA) at the level of the third lumbar vertebral (L3) or the third cervical vertebra (C3), bioimpedance analysis and anthropometry have been reported [3].

The relationship between low skeletal muscle mass and increased postoperative complications and its negative influence on survival has been demonstrated in various surgical fields such as hepato-biliary, colon and lung surgery [4,5,6]. In oncologic head and neck surgery, the predictive value of low SMM for surgical complications and survival has also been reported, including its relevance to head and neck cancer (HNC) patients requiring complex free tissue transfer for reconstruction [7,8]. This group of patients as a whole is at risk for complications, but

individualized risk data are needed to be able to personalize treatment.

This review aims to analyze articles that have assessed the presence of low skeletal muscle mass in HNC free flap reconstruction surgery patients and to correlate this factor with postoperative complications.

## Materials and methods

This systematic review was carried out in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [9].

The evaluation of the scientific question was based on the PICO/PECO strategy [10]:

P—Patient/Problem—adult patients undergoing reconstructive free flap surgery after surgery for malignant head and neck tumors;

E—Exposure—Diagnosis of low skeletal muscle mass.

C—Control/ Comparison—Diagnosis of normal skeletal muscle mass.

O—Outcome—Influence of low skeletal muscle mass on postoperative complications.

**Abbreviations:** SMI, Skeletal muscle index; SMM, Skeletal muscle mass; HNC, Head and neck cancer; C3, Third cervical vertebra; L3, Third lumbar vertebra; CSMA, Cross-sectional muscle area; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RFFF, Radial forearm free flap; FFF, Fibula free flap.

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### Eligibility criteria

The following criteria were adopted for the inclusion of studies in this review:

1. Report must include complications of surgical interventions for malignant head and neck tumors in regards to the presence of low SMM, in patients aged 18 years or older.
2. Report must include the presence of the diagnosis of low SMM, in patients aged 18 years or older.
3. Skeletal muscle mass must be quantified in the cross-sectional area of skeletal muscles on abdominal CT or MRI at the level of the L3, or derived using CT or MRI imaging at the level of the C3.
4. The postoperative results must include at least one of the following outcomes: Clavien-Dindo classification of outcomes, postoperative complications, infectious complications, vascular complications, or death. The events can be early, late or both.
5. Only articles in the English language were included

### Exclusion criteria

The exclusion criteria were:

1. Reports involving benign head and neck tumors, thyroid cancer and surgeries of a different nature than head and neck.
2. Diagnosis of low SMM based on other imaging modalities than CT or MRI.
3. Low SMM secondary to other interventions (e.g. post-transplant, post-chemotherapy, recent major surgery).
4. Letters to editors, incomplete unpublished articles and research protocols.

### Types of studies

Retrospective and prospective cohort studies that compared head and neck surgery outcomes in patients with low and normal SMM were included.

### Data search strategy and literature review

Two independent reviewers (EA and LR) performed a systematic search of the PubMed and EMBASE databases; only articles in the English language were searched. The period sought database inception to the 1st of May 2023. The systematic review followed the PRISMA guidelines.

Using the PubMed search tool, we selected the MeSH terms of the most relevant publications to conduct a new search in order to obtain more articles that could potentially be included in this review.

PUBMED: ("Sarcopenia"[Mesh] OR "Muscular Atrophy"[Mesh] OR "Frailty"[Mesh] OR "Low skeletal muscle mass" OR "Malnutrition"[Mesh]) AND ("Head and Neck Neoplasms"[Mesh] OR "Squamous cell carcinoma of head and neck" [Mesh] OR "Head and Neck Neoplasms"[Mesh] OR "Otorhinolaryngology Surgical Procedures"[Mesh] OR "Oral Surgical Procedures"[Mesh] OR "Free, Flap"[Mesh] OR "Flap, microsurgical free"[MeSH]).

EMBASE: ('sarcopenia'/exp OR'sarcopenia' OR'muscular atrophy'/exp OR'muscular atrophy' OR'frailty'/exp OR'frailty') AND ('head and neck surgical procedures'/exp OR'head and neck cancer' /exp OR'head and neck cancer surgery').

Reference lists of the publications fulfilling the inclusion criteria were also searched in order to identify additional studies.

### Selection of studies and data extraction

The abstracts identified by the literature search were screened independently for inclusion and exclusion criteria by the two reviewers

(EA, LG). If an abstract was judged as potentially relevant, the full-text of the publication was screened. Disagreeing cases were resolved with a third reviewer (RB).

The main data for each article included in the review were extracted by a reviewer (EA). The following were tabled: article headline, authors, year of publication, country of origin, basic characteristics of the study populations, study design, study objectives, sample size, inclusion and exclusion criteria, gender, age, prevalence of low skeletal muscle mass, method used to diagnose low SMM, and the cutoff for low SMM of the chosen method, type of surgery, location of cancer, primary and secondary outcomes regarding the presence or absence of low SMM. The data were checked by another reviewer (LG).

### Statistical analysis

Heterogeneity measures were used to evaluate the studies,  $I^2$  measure, which indicates the variation in the association measure attributable to heterogeneity. Random effects regression model was used for the data analysis if the I-squared was above the 50 % threshold. Tau-squared was given as an estimator of the variance between studies in a random effect meta-analysis. The overall effect was assessed under the null hypothesis that the odds ratio (OR) = 1 (there is no effect between the exposure levels). The graphs of forest plot and funnel plot (to assess publication bias) were performed. The analyses were performed using the statistical software IBM SPSS statistics 29.

### Results

#### Selected studies

The search strategy resulted in 57 articles (Fig. 1). After removing duplicate articles, 26 remained. These underwent initial screening, focusing on headlines and abstracts. After this initial screening, 11 articles remained for evaluation of the full text. Six of these articles had the necessary characteristics for inclusion. These studies were all retrospective in nature and were published between 2019 and 2021.

#### Population characteristics

Five studies involved both soft tissue and osseous free flaps [8,11,12,13,14], one study involved just osseous tissue free flaps [7]. The total number of subjects evaluated was 1082, between low SMM and normal SMM. Table 1 summarizes the population characteristics of each study.

#### Criteria for the diagnosis of low skeletal muscle mass

The most widely used method for assessing muscle mass was computed tomography, with assessment of the skeletal muscle index at the level of the third lumbar vertebra and specific cutoff points for each sex [8,11,12,13,14]. Alwani et al. [8] determined low skeletal muscle as  $< 41.6 \text{ cm}^2/\text{m}^2$  for males and  $< 32.0 \text{ cm}^2/\text{m}^2$  for females. Makiguchi et al. [11] defined low SMM as  $\text{SMI} < 36.02 \text{ cm}^2/\text{m}^2$  in men and  $< 31.76 \text{ cm}^2/\text{m}^2$  in women and used SMI as a continuous variable.

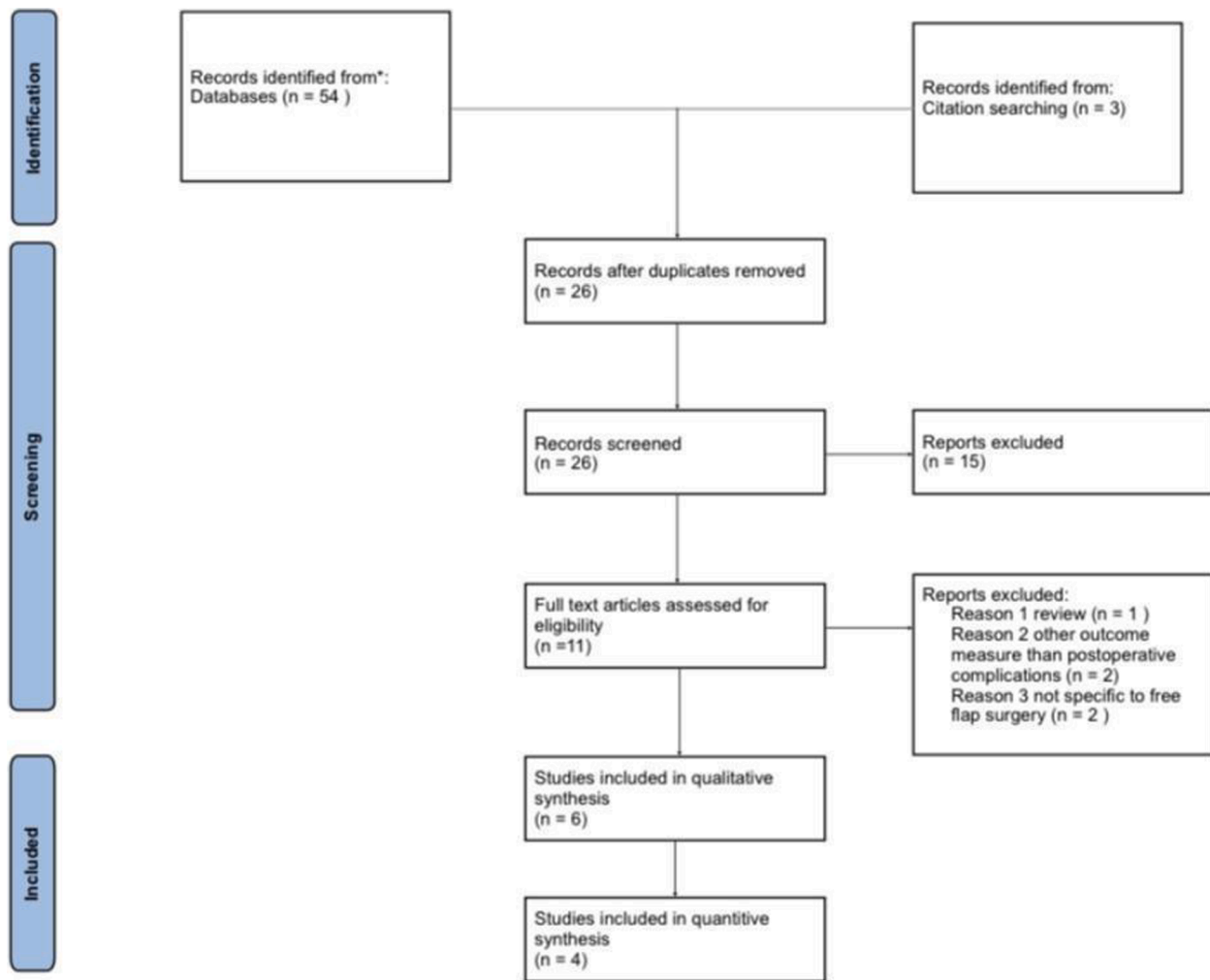
Ansari et al. and Chargini et al. measured SMM as the CSMA level of the third cervical vertebrae in both computed tomography and magnetic resonance imaging [7,14]. CSMA at the level of C3 was converted to CSMA at the level of L3 using a previously published formula [15]. Low SMM was defined as a SMI below  $43.2 \text{ cm}^2/\text{m}^2$ .

The prevalence of low skeletal muscle mass between studies ranged from 24.6% to 61.5%.

#### Outcomes

##### Low SMM and postoperative complications

In all six studies [7,8,11,12,13,14] an association was found between



**Fig. 1.** PRISMA flow-chart, describing the selection process. Studies were assessed by data-base screening and manual citation search. Duplicates were removed; studies not meeting the inclusion criteria were excluded. Of 11 studies eligible for analysis only 4 were suitable and included in quantitative synthesis.

low skeletal muscle mass and postoperative complications. To exclude the influence of other common factors in the study population, univariate and multivariate analyses were used. Alwani et al., [8] analyzed general ACS-NSQIP (American College of Surgeons National Surveillance and Quality Improvement Program) complications, and where they found that low SMM patients had greater rates of any general ACS-NSQIP complication (87.2 vs. 46.3%,  $p < 0.001$ , OR = 7.93), as well as a greater total number of general ACS-NSQIP complications (mean and standard deviation:  $2.47 \pm 1.92$  vs.  $1.05 \pm 1.52$ ,  $p < 0.001$ ). The authors also looked at Clavien–Dindo classification of surgical complications and flap-specific complications. They found a higher occurrence of fistula formation (27.7 vs. 12.4%,  $p = 0.022$ , OR = 2.70) and overall greater rates of any flap-specific complication (59.6 vs. 35.5%,  $p = 0.006$ , OR = 2.67) in the low SMM group.

Chargi et al., Ansari et al. [7,14] used the Clavien–Dindo classification of surgical complications to score the severity of all complications and also scored flap-related complications. Chargi et al. [14] found that low SMM in radial forearm free flap (RFFF) surgery is a predictor of postoperative complications (OR = 2.0, 95% CI 1.1–3.8,  $p = 0.03$ ). For fibula free flap (FFF) surgery, multivariate analysis distinguished the combination of elevated neutrophil–lymphocyte-ratio 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. Ansari et al. [7] reported that low SMM was associated with an increased risk of FFF related complications (HR 4.3;  $p = 0.02$ ) and severe postoperative complications (Clavien-Dindo grade III–IV) (HR 4.0;  $p = 0.02$ ).

Jones et al [11], investigated predictors of blood transfusion requirements in HNC free flap reconstruction patients. Multivariate regression determined low SMM ( $p = 0.023$ ), modified Charlson Comorbidity Index (mCCI) (OR = 1.49 95% CI 1.09–2.05,  $p = 0.013$ ), preoperative hemoglobin (OR = 3.34, 95% CI 1.18–9.46,  $p = 0.002$ ), operative time (OR = 1.003, 95% CI 1.000–1.007,  $p = 0.036$ ), and expected blood loss (OR = 1.006, 95% CI 1.003–1.009,  $P < 0.001$ ) as independent predictors of intraoperative transfusion requirements. A perioperative transfusion was also predicted by low SMM (OR = 2.83, 95% CI 1.17–6.86,  $p = 0.021$ ).

Makiguchi et al. [12,13] assessed the odds ratio of risk factors for surgical site infection and postoperative delirium in two separate reports. They concluded that lower SMM (OR = 2.52 per 10-unit decrease,  $p = 0.035$ ) increased the hypoactive and mixed types of postoperative delirium [13]. In the other article [12] they also looked at surgical site infection (SSI), where it was and concluded in a multiple logistic regression analysis, that lower SMI was an independent significant risk factor for recipient site SSI (adjusted OR (odds ratio) = 1.41 per 5 cm<sup>2</sup>/m<sup>2</sup> decrease,  $p = 0.015$ ).

#### Low SMM and hospital stay

One article [14] reported on the relationship between low SMM and hospital discharge in patients after HNC free flap reconstruction. Chargi et al. showed that when comparing mean hospital stay between patients with and without low SMM, patients with low SMM had comparable (16.6 days, SD 10.5 days) outcomes with patients without low SMM

**Table 1**  
Population characteristics of the 6 selected studies.

Author, year	Study design	Free flap type	Tumor location	Number of patients	Low SMM prevalence	Age (mean)	Method	SMI (cm <sup>2</sup> /m <sup>2</sup> ) cutoff
Alwani 2020	retrospective	ALT (35.1 %) RFFF (25.0 %) FFF (25.0 %) Other (14.9 %)	Aerodigestive tract (75.6 %) Other (24.4 %)	Male 120 (71.5 %) Female 48 (28.5 %)	47 (28.0 %)	59.4 (13) <sup>b</sup>	L3 skeletal muscle index (CT images)	<41.6 (male) <32.0 (female)
Ansari 2020	retrospective	FFF (100 %)	Oral cavity (100 %)	Male 54 (69.2) Female 24 (30.8)	48 (61.5 %)	62.4 (10.2) <sup>b</sup>	C3 skeletal muscle index (CT or MRI images)	<43.2 (male and female)
Chargi 2021	retrospective	RFFF <sup>1</sup> (48.0 %) FFF <sup>2</sup> (24.5 %) Other (27.4 %)	Oral cavity (93.4 %) Oropharynx (2.5 %) Neck (1.3 %) Paranasal sinus (0.7 %) Salivary gland (0.5 %) Skin (0.5 %) Nose(0.2 %) Hypopharynx (0.2 %)	Male 329 (59.4 %) Female 225 (40.6 %)	209 (37.7 %)	60.5 (51.7–69.4) <sup>a</sup>	C3 skeletal muscle index (CT or MRI images)	<43.2 (male and female)
Jones 2020	retrospective	ALT <sup>3</sup> (36.8 %) RFFF (26.8 %) FFF (19.7 %) Other (16.7 %)	Aerodigestive tract (72 %) Non-aerodigestive (28 %)	Male 163 (68.2 %) Female 76 (31.8 %)	62 (25.9 %)	60.4 (13.7) <sup>b</sup>	L3 skeletal muscle index (CT images)	<41.6 (male) <32.0 (female)
Makiguchi 2019	retrospective	RAM <sup>4</sup> (50 %) RFFF (45.1 %) FFF (2.5 %) LD <sup>5</sup> (2.5 %)	Tongue (46.7 %) Mandible (32.0 %) Oral floor (9.0 %) Buccal mucosa (7.4 %) Maxilla (4.9 %)	Male 82 (67.2 %) Female 40 (23.8 %)	39.9 (8.6) <sup>b</sup>	60.3 (11.2) <sup>b</sup>	L3 skeletal muscle index (CT images)	Continuous variable
Makiguchi 2020	retrospective	RAM (50 %) RFFF (45.1 %) FFF (2.5 %) LD (2.5 %)	Tongue (46.7 %) Mandible (32.0 %) Oral floor (9.0 %) Buccal mucosa (7.4 %) Maxilla (4.9 %)	Male 82 (67.2 %) Female 40 (23.8 %)	39.9 (8.6) <sup>b</sup>	60.3 (11.2) <sup>b</sup>	L3 skeletal muscle index (CT images)	Continuous variable

1 RFFF = Radial forearm free flap.

2 FFF = Fibula free flap.

3 ALT = Antero-lateral thigh free flap.

4 RAM = Rectus abdominis free flap.

5 LD = Latissimus dorsi free flap.

a median (IQR).

b mean (SD).

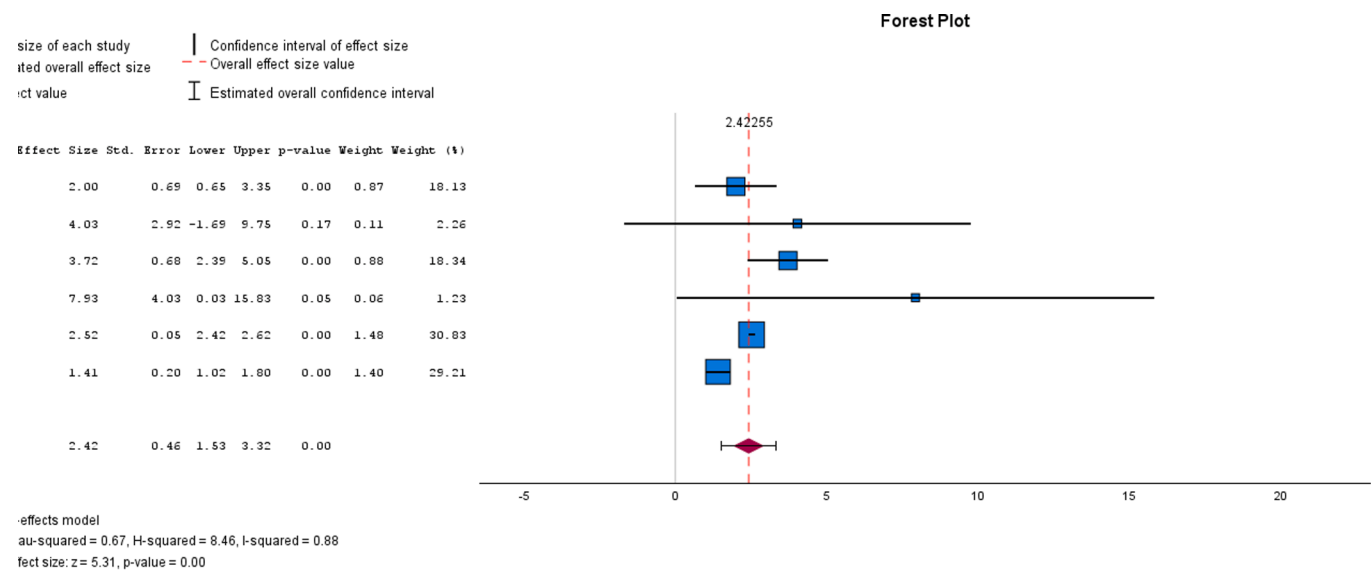


Fig. 2. Forest plot of the publications analyzed in relation to sarcopenia and post-surgical complications.

(15.7 days, SD 17.0 days) (mean difference 0.9 days, 95% CI 1.8–3.5,  $p = 0.5$ ).

Meta-analysis

Low skeletal muscle mass and postoperative complications

The meta-analysis corresponds to the assessment of low skeletal muscle mass as a risk factor for complications in patients undergoing HNC free flap reconstruction. After review, 4 publications were considered that reported the presence of low SMM as a dichotomous outcome and any postoperative complications. Of the 4 publications, 3 of them found the presence of low SMM as a risk factor for post-surgical complications ( $p < 0.05$ ).

The odds ratio (OR) values and their respective 95% confidence intervals (95% CI) were calculated. In Fig. 2, the forest plot is shown. The

global OR value was 2.42 ( $p = 0.00$ , 95% CI 1.53–3.32), indicating a significantly higher risk of any postoperative complications in patients with low SMM. The I-squared measure of heterogeneity was 0.88, a value determined as considerable heterogeneity. The publication bias was assessed using the funnel plot (Fig. 3). The graph represents each of the studies with the value of association and effect measures.

Discussion

This meta-analysis showed that low SMM is a predictive factor for any postoperative complications in HNC reconstructive surgery patients. These findings confirm other studies that demonstrate low SMM (and sarcopenia) as a factor with a worse prognosis. This may have important implications for the assessment of surgical risk and preoperative therapeutic management of HNC patients who need reconstructive surgery. In

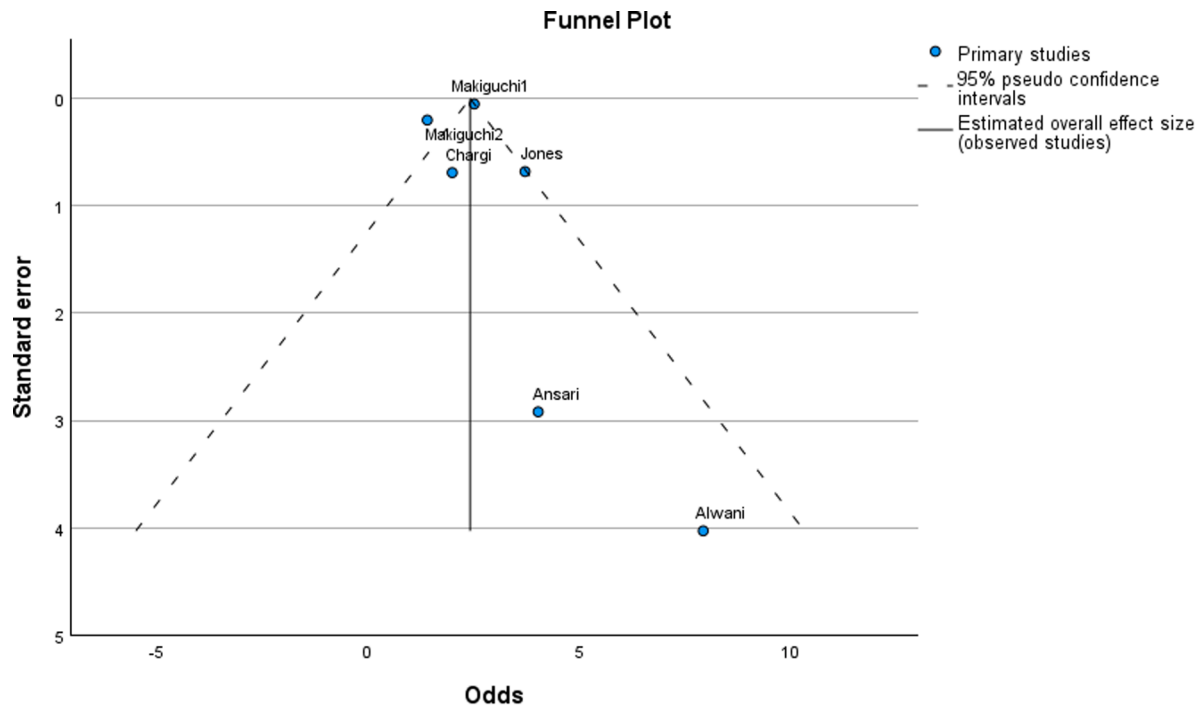


Fig. 3. Publication bias for studies that assessed sarcopenia as a factor associated with post-surgical complications.

the decision-making process of optimal flap choice, determining SMM could provide valuable information to aid surgical decision analysis and whether or not to opt for a direct microvascular reconstruction or alternative reconstruction or treatment. Although in HNC patients with low SMM a lower risk of complications might be expected if less extensive (reconstructive) surgery will be performed, no studies comparing standard and less extensive reconstructive procedures in these patients are reported yet. Information on a higher risk of complications in HNC patients with low SMM planned for microvascular reconstructive surgery can also be used to take perioperative supportive measures.

Prehabilitation programs can improve surgical outcomes in a variety of surgical and medical disciplines [16,17,18,19,20]. It is therefore of interest to prospectively study the effects of prehabilitation on patients with low SMM undergoing a microvascular free flap reconstruction after ablative head and neck surgery.

Furthermore, the use of sarcopenia-enhancing drugs to correct pathological muscle loss and weakness prior to surgery are being investigated. Rooks et al. studied bimagrumab, a monoclonal antibody that blocks activin type II receptor (ActRII) to inhibit myostatin signaling and stimulate protein anabolism in a double-blind, placebo-controlled, randomized controlled trial in adults with sarcopenia [21]. Bimagrumab increases lean body mass and decreases fat body mass compared to placebo. However, the authors found that the changes in body composition did not translate into a significant improvement in muscle strength or mobility compared to patients who had adequate nutrition intake and exercise, further emphasizing the importance of diet and physical activity in treating sarcopenia.

Our meta-analysis has several limitations. This review included only retrospective studies, therefore our meta-analysis may be affected by the biases as present in the original studies. The analysis of the impact of low SMM on hospital stay after surgery was not possible, since there was only one reported study on this subject [14]. However, low SMM was reported to be a predictive factor for length of hospital stay in patients undergoing major head and neck surgery [22]. Of note, the  $I^2$  measure for all free flaps pooled was 0.88 with a funnel plot indicating evidence of high heterogeneity. This may be due to several factors. Fig. 3 demonstrates an asymmetric funnel plot due to the limited number of studies. Although multiple medical database libraries were queried, the possibility of unpublished data cannot be excluded. In addition, tumor location and free flap types varied; no subgroup analysis could be performed given the limited data. Furthermore no consistent method of defining the low SMM cutoff was used across all studies. We included studies using different methods for assessing SMM. Most of the studies using computed tomography used the L3 muscle area for acquiring the SMI, although other groups had used the C3 muscle area. L3 muscle area can be predicted reliably based on C3 muscle area measurements using a validated method [15]. The threshold for diagnosing sarcopenia differed between studies. The studies of Alwani et al. and Jones et al. [8,11] used cutoffs for low SMM based on data from a population study with sex-specific cutoff values [23]. Others [7,14] used data based on a separate cohort of HNC patients [15]. The articles of Makiguchi et al [12,13] assumed that the SMI cutoffs proposed in Western studies were inappropriate for the Asian population due to differences in weight, lifestyle, and ethnicity. Given the difficulty of establishing a cutoff in this population, the authors treated SMI as a continuous value.

In conclusion, the results of our meta-analysis show that low SMM is associated with an increase in postoperative complications of HNC free flap surgery. We believe that the implementation of preoperative protocols that include tests for the diagnosis of low SMM should aid in selecting appropriate procedures to reduce postoperative complications. Future studies will also help to determine the role of preoperative interventions such as prehabilitation and sarcopenia enhancing medication.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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