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ORIGINAL ARTICLE – HEAD AND NECK ONCOLOGY

Prevalence and Association of Sarcopenia with Mortality in Patients with Head and Neck Cancer: A Systematic Review and Meta-Analysis

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ABSTRACT

Background. The objective of this meta-analysis was to assess the association of sarcopenia defined on computed tomography (CT) head and neck with survival in head and neck cancer patients.

Methods. Following a PROSPERO-registered protocol, two blinded reviewers extracted data and evaluated the quality of the included studies using the Quality In Prognostic Studies (QUIPS) tool, in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The quality of evidence was assessed using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) framework. A meta-analysis was conducted using maximally adjusted hazard ratios (HRs) with the random-effects model. Heterogeneity was measured using the I^2 statistic and was investigated using meta-regression and subgroup analyses where appropriate.

Results. From 37 studies (11,181 participants), sarcopenia was associated with poorer overall survival (HR 2.11, 95% confidence interval [CI] 1.81–2.45; $p < 0.01$), disease-free survival (HR 1.76, 95% CI 1.38–2.24; $p < 0.01$), disease-specific survival (HR 2.65, 95% CI 1.80–3.90; $p < 0.01$), progression-free survival (HR 2.24, 95% CI 1.21–4.13; $p < 0.01$) and increased chemotherapy or radiotherapy toxicity (risk ratio 2.28, 95% CI 1.31–3.95; $p < 0.01$). The observed association between sarcopenia and overall survival remained significant across different locations of cancer, treatment modality, tumor stages and geographical region, and did not differ between univariate and multivariate HRs. Statistically significant correlations were observed between the C3 and L3 cross-sectional area, skeletal muscle mass, and skeletal muscle index.

Conclusions. Among patients with head and neck cancers, CT-defined sarcopenia was consistently associated with poorer survival and greater toxicity.

Jin Hean Koh, Claire Yi Jia Lim, and Lucas Tze Peng Tan have contributed equally to this manuscript.

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Sarcopenia is an age-related syndrome characterized by loss of skeletal muscle mass (SMM), strength and function, and is associated with frailty, functional decline, falls, and mortality.[1] Clinically, sarcopenia is defined by low muscle strength, low muscle quantity or quality, and/or low physical performance.[1] Sarcopenia can also be quantified through imaging methods such as dual-energy x-ray absorptiometry (DEXA), computed tomography (CT), and magnetic resonance imaging (MRI).[2,3] Imaging modalities allow precise measurements that enable segmental and total muscle mass to be calculated and assessment of a muscle's fat infiltration, which influences force development and muscle quality. Current radiological definitions of sarcopenia recommended by the European, Asian, and international working groups utilize DEXA of the limbs, which is favored due to its low ionizing radiation dose and ability to investigate specific regions.[1]

Apart from DEXA, other methods, including CT and MRI, may be used in quantifying sarcopenia. Despite MRI being a promising technique, its use is limited in clinical practice. It is confined to research due to its high cost, lengthy acquisition, and inadequate cut-off values and standardized protocol.[2] Therefore, CT is commonly the first-line diagnostic modality that is frequently utilized in both oncological and non-oncological settings.[3] It has been demonstrated that CT can provide estimated quantification of skeletal muscle as there is a strong correlation between CT-derived values obtained from a single CT cross-sectional image and whole-body skeletal muscle.[4]

SMM may be assessed on CT imaging at the L3 vertebra level, with the L3 cross-sectional muscle area (CSMA) demonstrating excellent correlation with whole-body SMM.[5,6] In practice however, such abdominal scans are not routinely performed in head and neck cancer (HNC) patients and are often available only in locally advanced disease, with up to 93% of HNC patients lacking abdominal CT imaging.[7,8] Therefore, measurement of SMM at the third cervical vertebrae has been developed to overcome this limitation, demonstrating good correlation with CSA at the L3 level and providing a reliable approximation of total SMM.[9,10] Such an assessment may provide a means of screening for SMM and sarcopenia in HNC patients, without generating additional costs or burden for the individual patient.

Published data have reported an association between radiologically defined sarcopenia and adverse oncologic outcomes, including poorer survival in HNC patients.[2,11] Since then, several studies have sought to investigate the prognostic value of CT-defined sarcopenia at the C3 vertebra level for HNCs.[12–14] Such an assessment of SMM may provide a cost effective, efficient means of prognosticating outcomes in HNC patients. Therefore, this study aims to investigate the prognostic value of CT-defined sarcopenia at the C3 vertebra level in HNC patients. The hypothesis is that CT-defined sarcopenia at the C3 vertebra level and above is only prognostic of survival and unfavorable outcomes in HNCs.

METHODS

The prespecified protocol for this review was registered on PROSPERO (CRD42023393555). With reference to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, a search was conducted on the Medline, Embase and Cochrane databases for studies published before 30 December 2023.[15] The search strategy used a combination of the following search terms: (sarcopenia) AND ((CT head) or (CT neck)). The full search strategy is included in Online Resource 1. The references of included articles were also screened manually for a comprehensive search.

Study Selection

Three authors (JHK, CL and LTPT) independently screened abstracts in a blinded manner to check the eligibility for inclusion, with disputes being resolved through consensus from a fourth independent author (BYQT). Retrospective and prospective cohort studies, cross-sectional studies, and randomized controlled trials were considered for inclusion. The inclusion criteria were (1) clinical studies that used CT head or CT neck for the measurement of sarcopenia in patients with HNC; (2) full-text studies; (3) published in a peer-reviewed journal; and (4) written in English. Only studies that used muscle assessments at the C3 vertebrae level, or converted C3 measurements to an estimated L3 measurement, were included.

The exclusion criteria were (1) clinical studies that used MRI head or MRI neck for the measurement of sarcopenia in patients with HNC; (2) animal studies; (3) cadaver studies; (4) case reports; (5) in vitro studies; and (6) reviews.

Data Extraction

Relevant data from included articles were extracted by a pair of independent authors (CYJL and LTPT) in a double-blinded fashion into a structured proforma. Study characteristics including first author, year of study completion, stage of cancer, region of cancer, treatment modality, definition of sarcopenia, sample size, mean age, sex, BMI, Charlson Comorbidity Index (CCI) score, and smoking status were extracted. The primary outcomes of interest were overall survival (OS), disease-free survival (DFS), progression-free survival (PFS), and disease-specific survival (DSS), while

secondary outcomes included chemotherapy or radiotherapy toxicity, prevalence of sarcopenia, and correlations of different measurements of sarcopenia.

Quality Assessment

Quality assessment of the included articles was performed using the Quality In Prognostic Studies (QUIPS) tool. The QUIPS rates the risk of bias of cohort studies on the premises of appropriateness of sample frame, sampling method, ascertainment of exposure, demonstration that the outcome of interest was not present at the start of the study, comparability of cohorts, methods for assessment of outcomes, duration of follow-up, and adequacy of follow-up.[16] Publication bias was assessed by visual inspection of the respective funnel plots and Egger's test.[17,18]

Statistical Analysis

All analyses were conducted in R Studio (version 4.2.2; The R Foundation for Statistical Computing, Vienna, Austria) using the *meta* package.[19] Descriptive statistics were presented as means and standard deviations for continuous variables, and counts for categorical variables. Medians and interquartile ranges were converted to means and standard deviations using the published methods of Wan et al.[20]

A conventional pairwise meta-analysis was conducted using maximally adjusted hazard ratios (HRs) using the inverse variance method. Risk ratios were calculated for the categorical outcomes of chemotherapy and radiotherapy toxicities. Statistical heterogeneity was assessed via I^2 and Cochran Q test values, where an I^2 value of $<25\%$ representing low heterogeneity and an I^2 value $\geq 25\%$ representing moderate to high heterogeneity.[21,22] A Cochran Q test with a p value of ≤ 0.10 was considered significant for heterogeneity. Random-effects models were used in all analyses regardless of heterogeneity, as published evidence suggests that it provides more robust outcome measures compared with the alternative fixed-effects models.[23] When three of more studies were available, 95% prediction intervals (PIs) were computed to estimate the potential range of true effect sizes across individual studies, given that the 95% confidence interval (CI) only accounts for the uncertainty of the mean effect size, not the uncertainty of interstudy variance.[24] A meta-analysis of correlation coefficients was performed using the DerSimonian–Laird random-effects model.

Where 10 or more studies were available for a particular outcome, additional analyses were conducted to evaluate potential sources of heterogeneity between studies.[25] Apart from subgroup analyses, univariate random-effects meta-regression were conducted, and effect moderators were confirmed using permutation testing with 1000 iterations to eliminate spurious results.[26,27] Statistical significance was considered for outcomes with a p value ≤ 0.05. Publication bias was assessed through visual inspection of the funnel plots, with missing studies imputed using the trim-and-fill method.[28] Leave-one-out influence analyses were performed to examine the influence of individual studies on the overall findings. Cumulative meta-analyses were performed, ranked by year published, to examine the stability of published data over time.

Certainty of Evidence

The quality of pooled evidence was evaluated using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) framework.[29]

RESULTS

Literature Search

Details of the study selection process are summarized in Fig. 1. Overall, 1625 articles were included in the initial search after removal of duplicates, of which 61 were selected for full-text review; 37 articles met the final inclusion criteria.

Study Characteristics

Of the 37 included studies, 34 were retrospective cohort studies[9,12,13,30–56] and 3 were prospective cohort studies.[14,57,58] The total sample size was 11,181 patients. The mean age, BMI, and follow-up time was 58.56 ± 12.46 years, 21.61 ± 7.99 kg/m^2, and 36.43 ± 27.69 months; 70% of patients were male. 22 studies measured sarcopenia at the C3 vertebra level,[12–14,30–39,41–43,51,53–55,57,58] while 15 studies measured sarcopenia at the L3 vertebra level as converted from C3 skeletal muscle measurements.[9,40,44–50,52,56,59–62] Cut-off points varied by study and are found in Tables 1 and 2, which also contain a summary of the key characteristics for included articles. Within the included studies, cut-off values for defining sarcopenia were calculated from receiver operating characteristic (ROC) analyses or through published definitions of sarcopenia.[63,64] Details of the quality assessment of the included articles are shown in Online Resource 2.

Meta-Analysis for Overall Survival

The OS was reported in 21 studies (7562 participants).[12–14,35,36,39–41,44,45,47,48,51,52,54,55,57,59–62] Based on the random-effects model, OS was significantly lower in patients with sarcopenia compared with patients without sarcopenia (HR 2.11, 95% CI 1.81–2.45; $p < 0.01$, $I^2 = 45\%$) (see Fig. 2). Covariates adjusted for included age (13

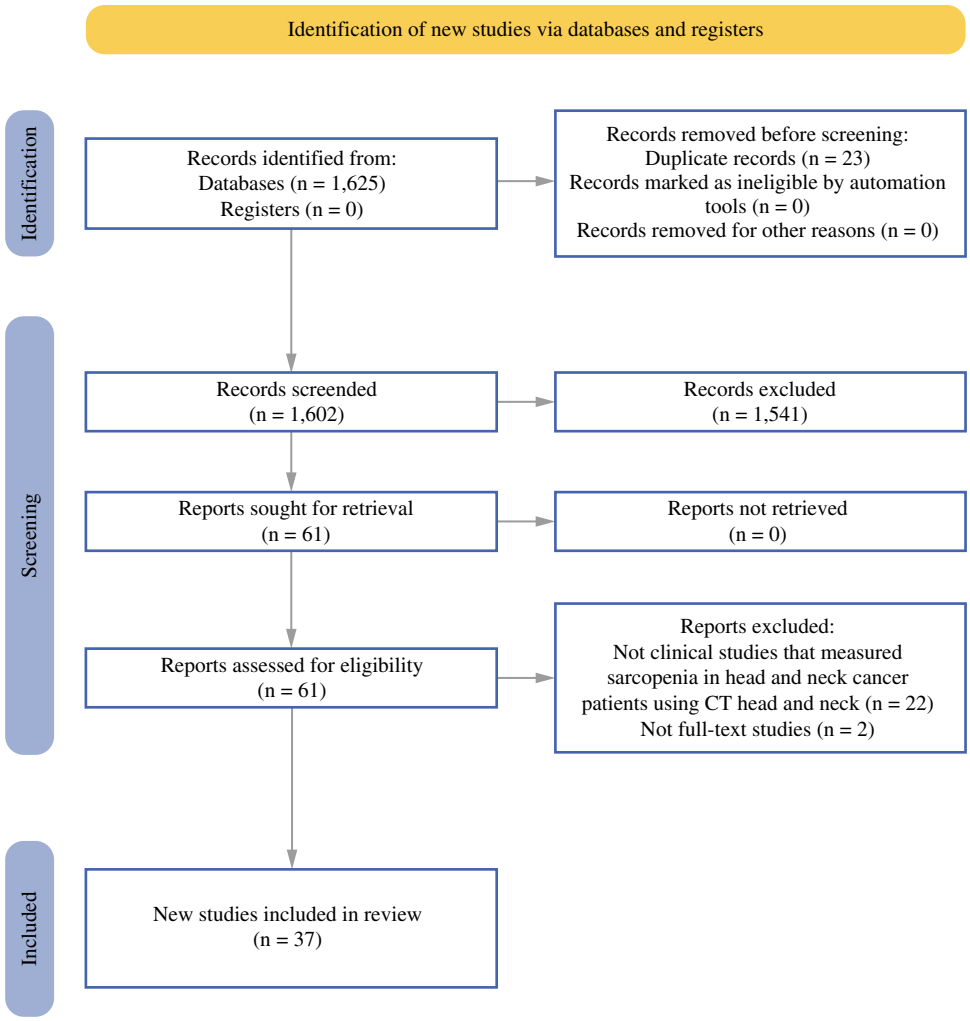

FIG. 1 PRISMA flow diagram. *CT* computed tomography, *PRISMA* Preferred Reporting Items for Systematic Reviews and Meta-Analyses

studies),[12–14,35,40,41,44,45,47,48,54,59,62] sex (4 studies),[35,40,45,54] stage of cancer (13 studies),[12–14,35,36,39,40,44,47,48,51,54,62] site of cancer (7 studies),[14,47,48,51,52,54,62] and BMI (5 studies).[35,40,41,45,51]

Given that the meta-analysis of sarcopenia and OS contained sufficient studies for further analyses, meta-regression was also performed to examine the influence of study-level covariates on OS. Meta-regression found that higher mean BMI significantly weakened the association between sarcopenia and OS, accounting for 100% of heterogeneity and leaving low (0.00%) residual heterogeneity. The pooled HR decreased by a factor of 0.25 (95% CI −0.36 to −0.14) per 1 kg/m^2 increase in mean BMI. The bubble plot is shown in Online Resource 3. Other characteristics, including mean age, year of study completion, sex (percentage of male patients), smoking status, and mean follow-up duration were not significant effect moderators of OS. The results of the meta-regression are shown in Online Resource 4.

Results of the subgroup analyses are shown in Online Resource 5. While the pooled association of sarcopenia with OS remained significant across studies with a mean BMI < 25 kg/m^2 (HR 3.00, 95% CI 2.40–3.75, I^2 = 0%)[13,14,35,40,51,52,55] and studies with a mean BMI ≥ 25 kg/m^2 (HR 1.52, 95% CI 1.29–1.79; I^2 = 0%)[,36,39,41,44,45,47,48,54,57] OS was significantly lower in studies with a mean BMI < 25 kg/m^2 (p < 0.01 for test of subgroup differences). The pooled association of sarcopenia with OS remained significant and similar across all subgroups of stage of cancer, including those for stage II–IV (HR 2.76, 95% CI 2.06–3.70; I^2 = 0%),[12,13,35] stage III–IV (HR 2.51, 95% CI 1.76–3.58; I^2 = 50%),[14,36,51] and stage I–IV cancers (HR 1.80, 95% CI 1.54–2.11; I^2 = 13%)[.40,41,44,45,47,48,52,57] The pooled association also remained significant among studies that adjusted for stage of cancer as a covariate (HR 2.15, 95% CI 1.78–2.61; I^2 = 51%)[14,35,36,39,40,44,47,51,54] and site of cancer as a covariate (HR 2.48, 95% CI 1.68 to 3.68; I^2 = 69%).[14,47,51,54] Adjustment for age, sex, and BMI did not influence the statistical significance of effect size of the pooled association, as shown from sensitivity analyses excluding studies that did not adjust for age, sex, or BMI. Further subgroup analyses demonstrated that the observed association of sarcopenia

TABLE 1 Characteristics of the included studies

Study	Stage of cancer	Region of cancer	Treatment	Definition of sarcopenia	Prediction model used
Bozkurt et al., *Ann Otol Rhinol Laryngol.*, 2018[30]	III–IV	Larynx	Surgery	Sarcopenia was defined at the C3 vertebrae level	Swartz
Bril et al., *Oral Oncol.*, 2021[31]	NR	Hypopharynx, larynx, oropharynx, oral cavity, nasopharynx	Treatment-naïve	Sarcopenia was defined at the C3 vertebrae level	Swartz
Casasayas et al., *Eur Arch Otorhinolaryngol.*, 2022[32]	NR	Larynx	Surgery	C3 CSMA < 35.5 cm^2	Swartz
Chang et al., *PLoS One.*, 2021[33]	I–IV	Hypopharynx, larynx, oropharynx, oral cavity	Treatment-naïve	M-SMI ≤ 52.4 cm^2 for males and ≤ 38.9 cm^2 for females	None
Endo et al., *Laryngoscope.*, 2021[34]	II–IV	Hypopharynx, larynx, oropharynx	CRT	Predicted C3 CSMA < 12.3 cm^2/m^2	None
Ganju et al., *Radiother Oncol.*, 2019[12]	II–IV	Hypopharynx, larynx, oropharynx	CRT	Predicted C3 CSMA < 41 cm^2/m^2 for females, and < 43 cm^2/m^2 if BMI < 25 for males and < 53 if BMI > 25 for males	Swartz
Haehl et al., *Cancers.*, 2022[59]	I–IV	Hypopharynx, larynx, oropharynx, oral cavity, nasopharynx	CRT	L3 SMI of ≤ 45.5 cm^2/m^2 in males and ≤ 34.3 cm^2/m^2 in females	
Hua et al., *Front Oncol.,* 2021[13]	II–IV	Nasopharynx	CRT	Predicted C3 SMI < 22.00 cm^2/m^2 for males and < 18.61 cm^2/m^2 for females	Swartz
Hua et al., *Ther Adv Med Oncol.*, 2020[35]	II–IV	Nasopharynx	CRT	Predicted C3 SMI ≤ 18.82 cm^2/m^2	Swartz
Huang et al., *Cancers (Basel).,* 2022[36]	III–IV	Oral cavity	Surgery	C3 SMI < 46.7 cm^2/m^2 for males and < 30.3 cm^2/m^2 for females	Swartz
Jin et al., *Cureus.*, 2022[37]	I–IV	Hypopharynx, larynx, oropharynx, oral cavity, salivary gland	CRT	SCM and posterior neck combined muscle index < 9.3 mm^2/m^2	None
Jung et al., *Oral Oncol*ogy., 2019[14]	III–IV	Hypopharynx, larynx, oropharynx, oral cavity	Surgery	Predicted C3 SMM < 56.3 cm^2	Swartz
Karavolia et al., *Radiotherapy and Oncology.*, 2022[38]	I–IV	Larynx	CRT	C3 SMI < 42.0 cm^2/m^2 for males and < 31.2 cm^2/m^2 for females	Wendrich
Lin et al., *Clin Otolaryngol.,* 2020[39]	NR	Oral cavity	Surgery	Predicted C3 SMM < 47.5 cm^2/m^2	Swartz
Lu et al., *Oral Dis.*, 2021[40]	I–IV	Oral cavity	Treatment-naïve	Actual L3 SMI < 55.0 cm^2/m^2 for males and 36.6 cm^2/m^2 for females	None
Mascarella et al., *Head Neck.*, 2022[58]	I–IV	Hypopharynx, larynx, oropharynx, oral cavity	Surgery	Sarcopenia was defined at the C3 vertebrae level	Swartz
Mascarella et al., *Microsurgery.*, 2022[57]	I–IV	Hypopharynx, larynx, oropharynx, oral cavity	Treatment-naïve	CPSMI < 1100 mm/m^2 for males and < 880 mm^2/m^2 for females	Swartz
McGoldrick et al., *Br J Oral Maxillofac Surg.*, 2022[41]	I–IV	Hypopharynx, larynx, oropharynx, oral cavity	Surgery	Sarcopenia was defined at the C3 vertebrae level	Swartz
Morelli et al., *Cancers.*, 2023[60]	III–IV	Hypopharynx, larynx, oropharynx, oral cavity	CRT	Estimated L3 SMI < 43.2 cm^2/m^2	Swartz
Morse et al., *Cancers.*, 2022[42]	III–IV	Hypopharynx, larynx, oropharynx	CRT	Sarcopenia was defined at the C3 vertebrae level	Swartz
Nagpal et al., *Oral Oncol.*, 2021[43]	III–IV	Oral cavity, oropharynx	CRT	Predicted C3 CSA < 32 cm^2/m^2	Swartz

Table 1 (continued)

Study	Stage of cancer	Region of cancer	Treatment	Definition of sarcopenia	Prediction model used
Naser et al., *Front Oncol.,* 2022[44]	I–IV	Oral cavity, oropharynx	CRT	Estimated L3 SMI < 52.4 cm^2/m^2 in males and 38.5 cm^2/m^2 in females	Swartz
Ohyama et al., *Oral Maxillofac Surg.,* 2023[61]	I–IV	Oral cavity	CRT	Estimated L3 SMI < 41.5 cm^2/m^2 in males and 26.6 cm^2/m^2 in females	None
Olson et al., *Front Oncol*., 2022[45]	I–IV	Larynx, oropharynx, oral cavity	Surgery	Estimated L3 SMI < 52.4 cm^2/m^2 in males and 38.5 cm^2/m^2 in females	Swartz
Swartz et al., *Oral Oncol*ogy., 2016[9]	III–IV	Oropharynx, nasopharynx	Treatment-naïve	Estimated L3 SMI	Swartz
Ufuk et al., *Clin Exp Otorhinolaryngol*., 2019[46]	I–IV	Hypopharynx, oropharynx, oral cavity, nasopharynx	CRT or surgery	L3 SMI of ≤ 52.4 cm^2/m^2 in males and ≤ 38.9 cm^2/m^2 in females	None
Van Heusden et al., *Quant Imaging Med Surg.,* 2022[47]	I–IV	Hypopharynx, oropharynx, oral cavity, nasopharynx	CRT or surgery	L3 SMI < 43.2 cm^2 /m^2	None
Van Rijn-Dekker et al., *Radiotherapy and Oncology*., 2020[48]	I–IV	Hypopharynx, larynx, oropharynx, oral cavity, nasopharynx	CRT	Estimated L3 SMI < 42.4 cm^2/m^2 in males and < 30.6 cm^2/m^2 in females	Swartz
Vangelov et al., *Head Neck.,* 2022[49]	NR	Hypopharynx, larynx, oropharynx, oral cavity, nasopharynx	Treatment-naïve	Estimated L3 SMI < 41 cm^2/m^2 in females, and in males, < 43 cm^2/m^2 (underweight or healthy weight) and < 53 cm^2/m^2 (overweight or obese)	Swartz
Vangelov et al., *Eur Arch Otorhinolaryngol*., 2022[50]	NR	Hypopharynx, larynx, oropharynx, oral cavity, nasopharynx	Treatment-naïve	Estimated L3 SMI < 43 cm^2/m^2 (underweight or healthy weight) and < 53 cm^2/m^2 (overweight or obese) in males and < 41 cm^2/m^2 in females	Own model
Wendrich et al., *Oral Oncol*., 2017[51]	III–IV	Hypopharynx, larynx, oropharynx, nasopharynx	CRT	Estimated C3 SMM ≤ 43.2 cm^2/m^2	Swartz
Yamahara et al., *Auris Nasus Larynx*., 2021[52]	I–IV	Hypopharynx, larynx, oropharynx, oral cavity, nasopharynx	CRT or surgery	Estimated L3 SMI < 43.2 cm^2/m^2	Swartz
Ye et al., *JAMA Netw Open*., 2023[62]	I–IV	Oropharynx, larynx/hypopharynx	CRT	Estimated L3 SMI < 52.4 cm^2/m^2 in males and 38.5 cm^2/m^2 in females	Swartz
Yoon et al., *PLoS One*., 2021[53]	I–IV	Hypopharynx, larynx, oropharynx, oral cavity, nasopharynx	Treatment-naïve	Estimated C3 SMM < 49 cm^2/m^2 for males and < 31 cm^2/m^2 for females	None
Yoshimura et al., *Cancers (Basel).,* 2021[54]	NR	Oral cavity	Surgery	SCMI < 1.831 in males and < 1.562 in females	None
Yunaiyama et al., *Eur Arch Otorhinolaryngol*., 2022[55]	NR	Hypopharynx, larynx, oropharynx, nasopharynx	CRT	Estimated IHSMI < 16.88 cm^2/m^2	None
Zwart et al., *J Cachexia Sarcopenia Muscle.,* 2019[56]	III–IV	Hypopharynx, larynx, oropharynx, oral cavity	Treatment-naïve	Estimated L3 SMI < 43.2 cm^2/m^2	Swartz

BMI body mass index, *CPSMI* cervical paraspinal skeletal muscle index, *CSA* cross-section area, *CSMA* cross-sectional muscle area, *CRT* chemoradiotherapy, *IHSMI* infrahyoid skeletal muscle index, *M-SMI* masticatory skeletal muscle index, *NR* not reported, *SCM* sternocleidomastoid, *SCMI* sternocleidomastoid muscle index, *SMI* skeletal muscle index, *SMM* skeletal muscle mass

TABLE 2 Patient characteristics

Study	Sample size	Age (years)	Sex (% male)	BMI (kg/m^2)	CCI		Smoking status		Covariates
					<5	≥5	Ever	Never	
Bozkurt et al., *Ann Otol Rhinol Laryngol*., 2018[30]	60	59.37 ± 8.40	100	23.57 ± 5.13	37	23	58	2	NA
Bril et al., *Oral Oncol*., 2021[31]	200	63.5 ± 8.30	74	24.2 ± 4.60	NR	NR	NR	NR	NA
Casasayas et al., *Eur Arch Otorhinolaryngol*., 2022[32]	86	65.7 ± 10.30	100	25.4 ± 4.70	NR	NR	NR	NR	NA
Chang et al., *PLoS One*., 2021[33]	102	67.2 ± 16.40	85	26.05 ± 2.21	NR	NR	NR	NR	NA
Endo et al., *Laryngoscope*., 2021[34]	159	64.5 ± 7.90	89	22.03 ± 3.74	NR	NR	141	18	NA
Ganju et al., *Radiother Oncol*., 2019[12]	246	56.75 ± 12.31	81	NR	NR	NR	177	69	Age, tumor stage, concurrent cisplatin
Haehl et al., *Cancers*., 2022[59]	280	NR	NR	NR	NR	NR	69	39	Age, smoking
Hua et al., *Front Oncol.,* 2021[13]	806	48 ± 10.43	75	23.45 ± 3.23	NR	NR	NR	NR	Age, tumor stage, histological type, EBV-DNA, hs-CRP
Hua et al., *Ther Adv Med Oncol*., 2020[35]	1170	47.29 ± 10.43	47	23.53 ± 2.96	NR	NR	NR	NR	Age, sex, tumor stage, BMI, histological type, EBV-DNA
Huang et al., *Cancers (Basel).,* 2022[36]	592	54.2 ± 11.00	88	25.3 ± 4.30	211	381	467	125	Tumor stage, neutrophil-to-lymphocyte ratio, PLR, systemic inflammation index
Jin et al., *Cureus*., 2022[37]	51	59 ± NR	82	25.83 ± 2.68	NR	NR	NR	NR	NA
Jung et al., *Oral Oncology*., 2019[14]	305	64.33 ± 12.66	87	23.1 ± 3.35	302	1	NR	NR	Age, tumor stage, tumor site, CCI, frailty, Karnofsky performance status
Karavolia et al., *Radiotherapy and Oncology*., 2022[38]	977	64 ± 10.14	69	22.5 ± 4.25	NR	NR	977	NR	NA
Lin et al., *Clin Otolaryngol.,* 2020[39]	276	55 ± 12.00	77	25 ± 5.00	NR	NR	NR	NR	Tumor stage
Lu et al., *Oral Dis*., 2021[40]	220	55.58 ± 40.73	72	22.1 ± 3.40	NR	NR	NR	NR	Age, sex, tumor stage, BMI, malnutrition, tumor grade
Mascarella et al., *Head Neck*., 2022[58]	127	61.8 ± 14.10	67	26.4 ± 7.10	NR	NR	127	NR	Age, sex, tumor stage, CCI, preoperative serum albumin
Mascarella et al., *Microsurgery*., 2022[57]	127	62.56 ± 12.88	68	26.71 ± NR	NR	NR	NR	NR	NA
McGoldrick et al., *Br J Oral Maxillofac Surg*., 2022[41]	111	74 ± 5.32	69	NR	NR	NR	NR	NR	Age, sex, tumor stage, tumor site
Morelli et al., *Cancers*., 2023[60]	115	31.38 ± 5	79	NR	NR	NR	96	19	Unadjusted
Morse et al., *Cancers*., 2022[42]	272	NR	82	NR	NR	NR	191	81	Age, ECOG-PS, smoking, BMI, SMI, SMG, pretreatment albumin
Nagpal et al., *Oral Oncol*., 2021[43]	300	60.4 ± NR	88	NR	NR	NR	300	NR	Unadjusted
Naser et al., *Front Oncol.,* 2022[44]	409	57.25 ± 10.01	86	NR	NR	NR	NR	NR	Unadjusted

Table 2 (continued)

Study	Sample size	Age (years)	Sex (% male)	BMI (kg/m^2)	CCI		Smoking status		Covariates
					<5	≥5	Ever	Never	
Ohyama et al., *Oral Maxillofac Surg.*, 2023[61]	146	69.90 ± 7.04	46	NR	NR	NR	NR	NR	Unadjusted
Olson et al., *Front Oncol.*, 2022[45]	536	64 ± 11.89	62	NR	NR	NR	NR	NR	Age, tumor stage feeding tube, perineural invasion
Swartz et al., *Oral Oncology.*, 2016[9]	103	61.9 ± 10.50	72	24.8 ± NR	NR	NR	NR	NR	Age, sex, C3 CSA, weight
Ufuk et al., *Clin Exp Otorhinolaryngol.*, 2019[46]	159	62.2 ± 12.10	54	25.6 ± 5.70	NR	NR	NR	NR	Age, weight, BMI
Van Heusden et al., *Quant Imaging Med Surg.*, 2022[47]	99	61.71 ± 8.63	73	NR	NR	NR	83	13	CCI, low MSMI, low LSMI, C3 CSA
Van Rijn-Dekker et al., *Radiotherapy and Oncology.*, 2020[48]	744	63.02 ± 10.14	75	25.6 ± NR	NR	NR	676	66	Age, tumor stage, WHO PS, smoking history, P16 status, tumor site, treatment modality
Vangelov et al., *Head Neck.*, 2022[49]	101	60.6 ± 10.20	83	27.4 ± 5.40	NR	NR	NR	NR	NA
Vangelov et al., *Eur Arch Otorhinolaryngol.*, 2022[50]	109	61 ± 10.40	85	27* ± NR	NR	NR	NR	NR	C3 CSA, age, sex, baseline weight
Wendrich et al., *Oral Oncol.*, 2017[51]	112	54.5 ± 9.40	64	23.04 ± 3.96	NR	NR	94	18	BMI, lumbar SMI, chemotherapy dose
Yamahara et al., *Auris Nasus Larynx.*, 2021[52]	164	69.25 ± 9.55	87	21.6 ± 3.48	NR	NR	NR	NR	Tumor stage, tumor site, treatment, Hb, BMI, PLR
Ye et al., *JAMA Netw Open.*, 2023[62]	342	NR	83	NR	NR	NR	217	123	Age, smoking, tumor stage, tumor site
Yoon et al., *PLoS One.*, 2021[53]	165	60.4 ± 12.20	83	23.54 ± NR	NR	NR	NR	NR	NA
Yoshimura et al., *Cancers (Basel).*, 2021[54]	102	66.67 ± 3.76	58	NR	NR	NR	NR	NR	Age, sex, comorbidities, psoas muscle index, SCMI, intramuscular adipose tissue content, processus spinosus muscle-intramuscular adipose tissue content
Yunaiyama et al., *Eur Arch Otorhinolaryngol.*, 2022[55]	101	61.3 ± 43.69	85	22.21 ± 12.96	NR	NR	NR	NR	Age, sex, treatment modality, tumor site, tumor stage, extranodal spread
Zwart et al., *J Cachexia Sarcopenia Muscle.*, 2019[56]	112	63.2 ± 9.20	73	24.43 ± 1.20	NR	NR	103	9	Frailty, malnutrition

BMI body mass index, *CCI* Charlson-Comorbidity Index, *CSA* cross-section area, *EBV-DNA* Epstein–Barr DNA, *ECOG-PS* Eastern Cooperative Oncology Group performance status, *hs-CRP* high-sensitivity C-reactive protein, *LSMI* lumbar skeletal muscle index, *MSMI* masseter skeletal muscle index, *NA* not applicable, *NR* not reported, *PLR* platelet-to-lymphocyte ratio, *SCMI* sternocleidomastoid muscle index, *SMG* skeletal muscle gauge, *SMI* skeletal muscle index

with OS remained consistent across treatment modalities, geographical regions, use of prediction models for quantifying sarcopenia, cut-off values for sarcopenia (either ROC analysis or published definitions) and sites of cancer, which included nasopharyngeal, oral cavity, and mixed sites.

While visual inspection suggested funnel plot asymmetry, this was not suggested by Egger's test (intercept = 0.2268, 95% CI −1.10 to 0.32; $t = 0.52$, $p = 0.56$). Trim and fill imputed 10 studies (Online Resource 6) with minimal change to the pooled effect size (HR 2.31, 95% CI 1.85–2.76; $I^2 = 57\%$). Leave-one-out influence analysis showed that no

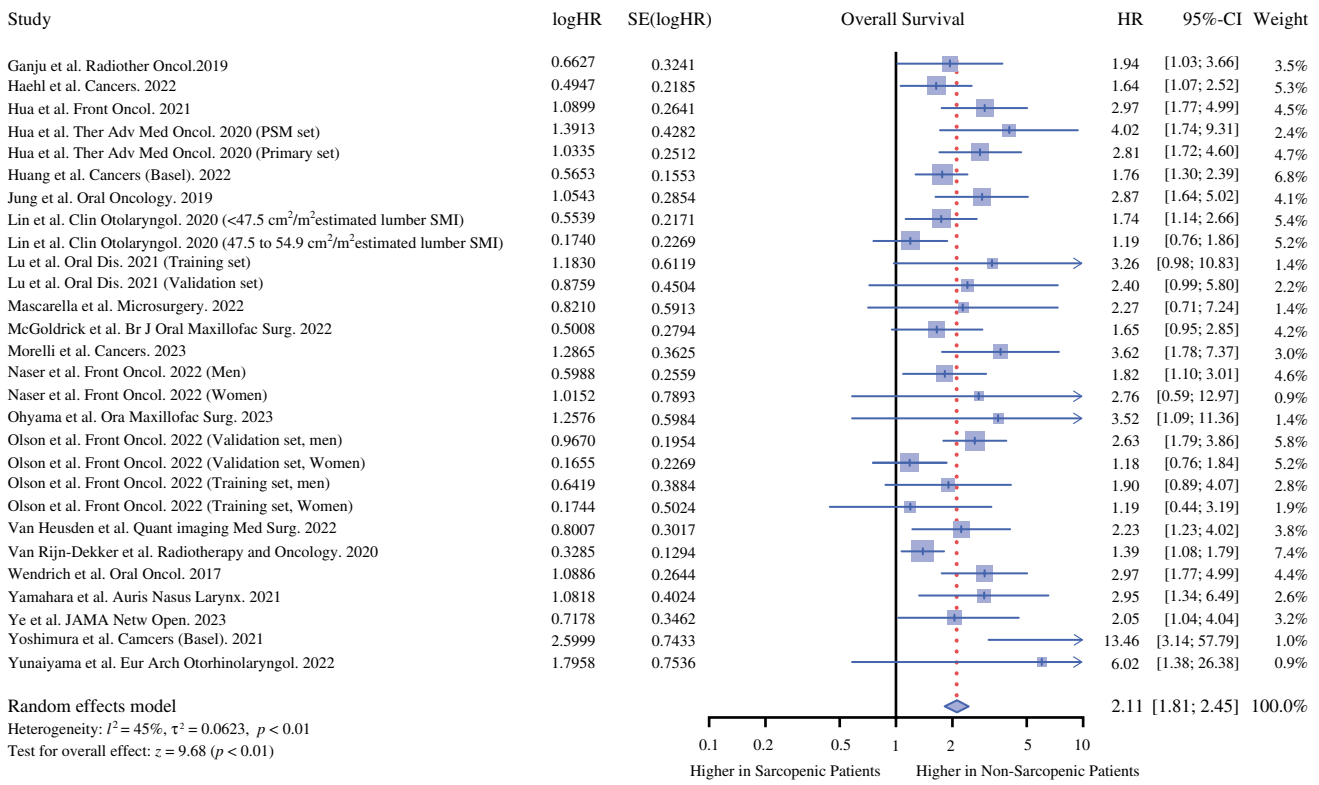

FIG. 2 Forest plot for OS. *OS* overall survival, *CI* confidence interval, *HR* hazard ratio, *SE* standard error

single study had a drastic change on the pooled HR (Online Resource 7), and cumulative meta-analysis showed a significant and stable pooled effect size since 2017 (Online Resource 8).

Disease-Free, Disease-Specific, and Progression-Free Survival

The DFS was reported in seven studies (3348 participants).[35,36,39,43,48,52,54] Based on the random-effects model, DFS was significantly lower in patients with sarcopenia compared with patients without sarcopenia (HR 1.76, 95% CI 1.38–2.24; $p < 0.01$, $I^2 = 62\%$) (see Fig. 3). Covariates adjusted for included age (two studies),[35,54] sex (two studies),[35,54] stage of cancer (four studies),[35,36,39,54] and site of cancer (one study).[54]

Results of the subgroup analyses are shown in Online Resource 9. The pooled association of sarcopenia with DFS remained significant among studies that adjusted for age, sex, stage of cancer, site of cancer, and BMI stage of cancer as a covariate.

The DSS and PFS were reported in four (885 participants)[45,54,55,61] and two (297 participants)[12,37] studies, respectively. Based on the random-effects model, DSS (HR 2.65, 95% CI 1.80–3.90; $p < 0.01$, $I^2 = 0\%$) and PFS (HR 2.24, 95% CI 1.21–4.13; $p < 0.01$, $I^2 = 0\%$) were significantly lower in patients with sarcopenia compared with patients without sarcopenia (see Fig. 4). Covariates adjusted for included age (three studies),[45,54,55] sex (two studies),[45,54] stage of cancer (three studies),[12,45,55] and site of cancer (one study).[55] Adjustment for age, sex, stage of cancer, and site of cancer did not influence the statistical significance of effect size of the pooled association (see Online Resource 9).

CHEMOTHERAPY OR RADIOTHERAPY TOXICITY

The chemotherapy or radiotherapy toxicity was reported in five studies (808 participants).[12,37,42,51,58] Based on the random-effects model, the risk of chemotherapy or radiotherapy toxicity was significantly higher in patients with sarcopenia compared with patients without sarcopenia (risk ratio 2.28, 95% CI 1.31–3.95; $p < 0.01$, $I^2 = 84\%$) (see Fig. 4).

Prevalence of Sarcopenia

The prevalence of sarcopenia among HNC patients was reported in 21 studies (6780 participants).[12,13,33,35–38,45,47–49,51–53,55,56,58–62] Based on the random-effects model, the prevalence of sarcopenia in HNC

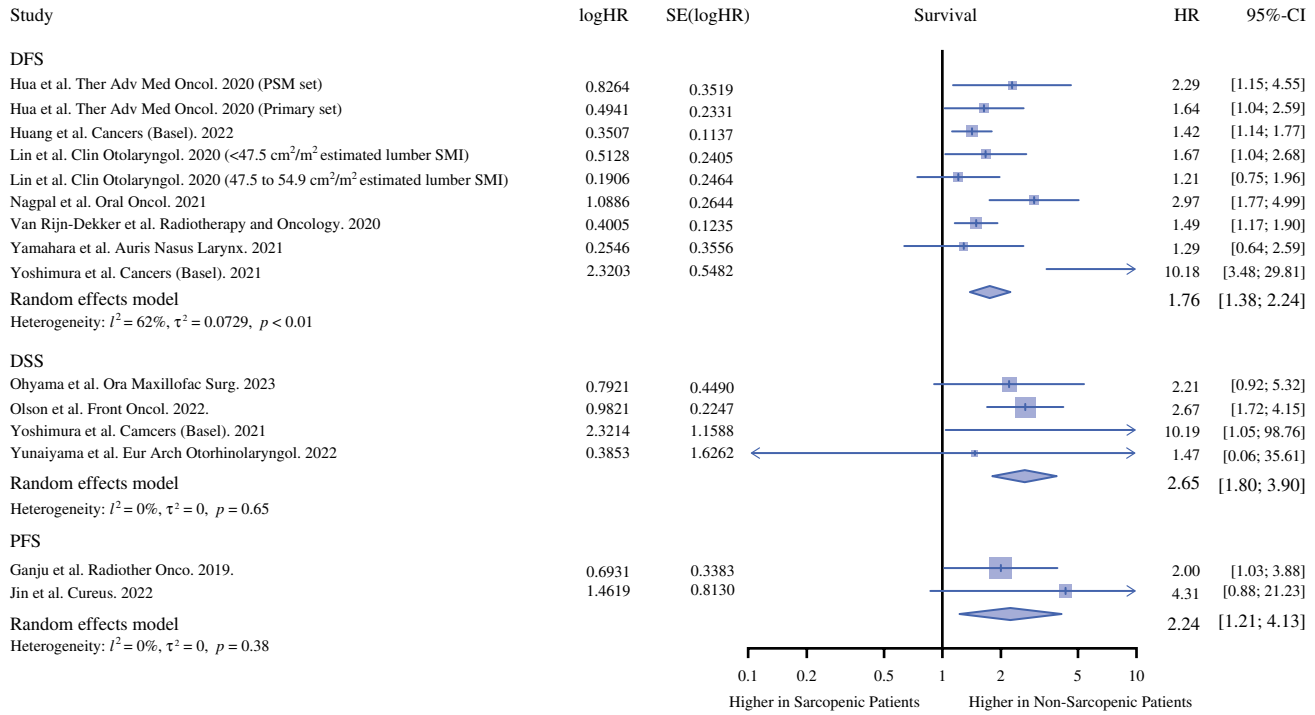

FIG. 3 Forest plot for DFS, DSS, and PFS. *DFS* disease-free survival, *DSS* disease-specific survival, *PFS* progression-free survival, *CI* confidence interval, *HR* hazard ratio, *SE* standard error

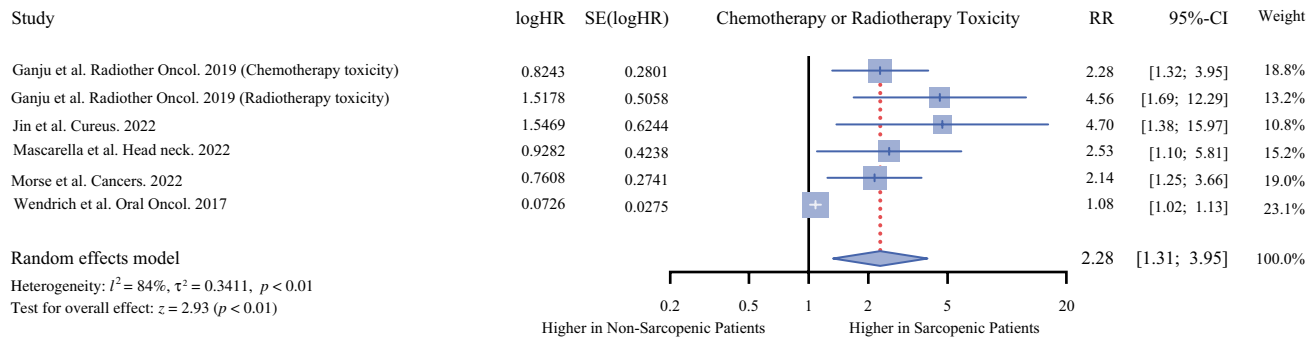

FIG. 4 Forest plot for chemotherapy or radiotherapy toxicity. *RR* risk ratio, *CI* confidence interval, *SE* standard error

patients was 50.78% (95% CI 42.52–59.02, $I^2 = 98\%$) (see Fig. 5).

Meta-regression found that study-level characteristics, including mean age, year of study completion, sex (percentage of male patients), mean BMI, mean follow-up duration, percentage of Asian patients, and percentage of Caucasian patients were not significant effect moderators of the prevalence of sarcopenia. The results of the meta-regression are shown in Online Resource 4.

Results of the subgroup analyses are shown in Online Resource 10. No significant differences in the pooled prevalence of sarcopenia were observed across all subgroups of stage of cancer, geographical region, site of cancer, and treatment modality.

While visual inspection suggested funnel plot asymmetry, this was not suggested by Egger's test (intercept = 0.5568, 95% CI −0.8812 to 0.7706; $t = 1.46$, $p = 0.17$). Trim and fill imputed nine studies (Online Resource 11) with minimal change to the pooled effect size (39.56, 95% CI 22.55–43.43; $I^2 = 52\%$). Leave-one-out influence analysis showed that no single study had a drastic change on the pooled prevalence (Online Resource 12), and cumulative meta-analysis showed a stable pooled effect size since 2017 (Online Resource 13).

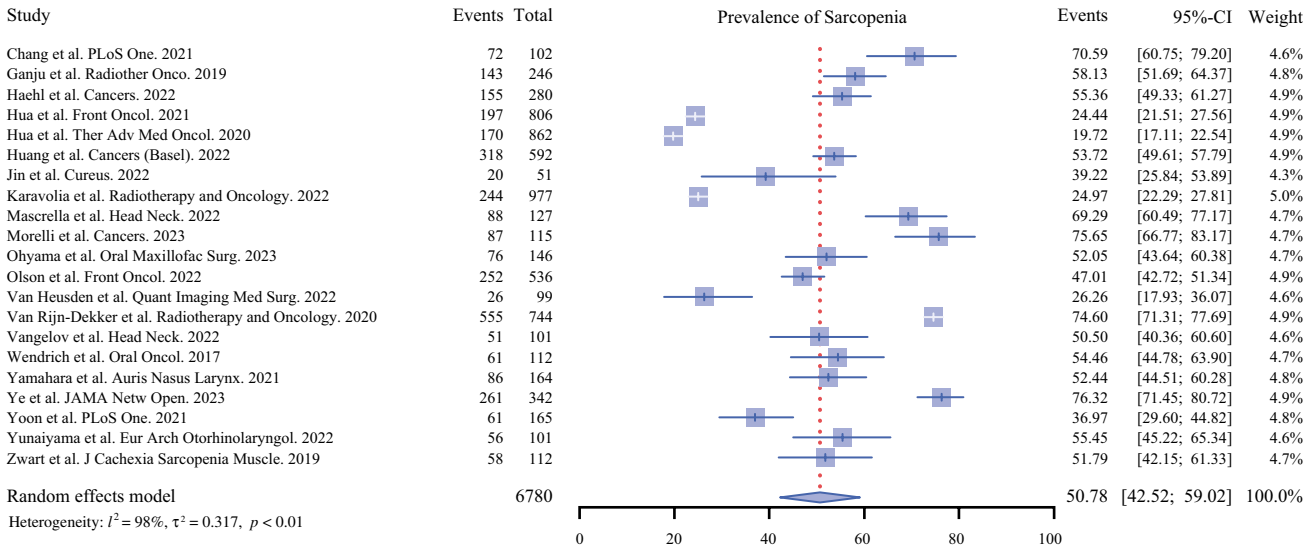

FIG. 5 Forest plot for prevalence of sarcopenia. *CI* confidence interval

TABLE 3 Results of the meta-analysis of correlations

Outcome	No. of studies (sample size)	r (95% CI)	*p* value
Correlation between C3 CSA and L3 CSA	6 (712)[9,31,40,47,49,50]	0.817 (0.740–0.873)	<0.01
Correlation between C3 SMI and L3 SMI	3 (860)[45,46,53]	0.729 (0.421–0.887)	<0.01

CI confidence interval, *CSA* cross-section area, *SMI* skeletal muscle index

Meta-Analysis of Correlations

The results of the meta-analysis of correlations are shown in Table 3. Statistically significant correlations were observed between C3 CSA and L3 CSA, and C3 SMI and L3 SMI.

Grading of Recommendations, Assessment, Development and Evaluations (GRADE) Quality of Evidence

The certainty of evidence for OS (moderate), DFS (low), PFS (low), DSS (low), chemotherapy or radiotherapy toxicity (low), and prevalence of sarcopenia (low) were assessed using the GRADE framework. The results of this assessment are shown in Online Resource 14.

DISCUSSION

In this systematic review and meta-analysis of 37 studies with 11,181 participants, with overall moderate-quality evidence, CT-defined sarcopenia was associated with poorer OS and DFS in patients with HNC. This association was consistent regardless of cancer stage, cancer site, treatment modality, and study location, but was weaker in studies with a higher mean BMI. One in every two patients with HNC were sarcopenic, and these patients also had double the risks of chemotherapy or radiotherapy toxicity compared with patients without sarcopenia.

In 2021, Wong et al. investigated the relationship between sarcopenia and OS in HNC patients, with sarcopenia defined at either the C3 or L3 level using either CT or MRI imaging.[11] Their study similarly revealed that radiologically defined sarcopenia was a negative predictor of OS in patients with HNC. Our meta-analysis updates the review by Wong et al. and further provides meta-analyses of the association of sarcopenia with DFS and PFS.[11] We have also included only clinical studies that quantified sarcopenia at the C3 vertebrae level. Our meta-analysis also demonstrated that the association of sarcopenia with OS remained significant across different subgroups of cancer stage, cancer location, geographical region, and treatment modality. Additional sensitivity analyses demonstrated that these findings were robust to publication bias, leave-one-out analyses, and cumulative analyses.

While radiographic sarcopenia has been traditionally diagnosed using L3 SMI, newer methods such as those proposed by Swartz et al. have converted C3 CSA to an estimated L3 SMI. As most HNC patients will receive a pretreatment CT of the head and neck, this represents an

expedient means of screening for sarcopenia in HNC patients. This method has been further validated in multiple other studies.[31,51,65,66] In this meta-analysis, most included studies utilized CT imaging to diagnose sarcopenia with the prediction model. There were studies that employed experimental methods, such as using C3 SMI alone, L3 psoas muscle index, or C3 sternocleidomastoid muscle index. However, it should be noted that the utility of these methodologies remain debated as there is currently no evidence supporting that the mass of a single muscle correlates with whole-body composition.

Investigation of sarcopenia in oncology patients is relevant to clinical practice given its potential value for prognostication of disease outcomes. Several reasons may explain why sarcopenia is a suitable prognostic indicator for patients with HNC. First, the vast majority of HNC patients receive a CT scan of the head and neck for disease staging and surveillance, therefore increasing the convenience of sarcopenia screening. Second, HNC patients also demonstrate poorer oncological outcomes in terms of decreased OS, DFS, and chemotherapy and radiotherapy toxicity.[11,67,68] Third, this meta-analysis has demonstrated a high prevalence of sarcopenia in patients with HNC, hence treatment of sarcopenia has the potential to improve patient outcomes in this field. Given that sarcopenia is a potentially modifiable risk factor in patients with HNCs, identification of sarcopenic patients may allow for early interventions to minimize treatment delays and improve outcomes.

Several mechanisms may explain how sarcopenia reduces OS in patients with cancer. Radiologically defined sarcopenia has been found to be a significant predictor of higher mortality and lower OS in other malignancies, including those of the breast, esophagus, and stomach. In breast cancer, sarcopenia was an independent predictor of negative outcomes, such as a twofold increased risk of dying from breast cancer-related pathologies.[69] A possible mechanism is greater drug toxicity, which in turn reduces effective oncologic therapy doses and increases the risk of postoperative complications, including infection and immobility.[11] Sarcopenia may also serve as an indicator of a patient's nutritional status. Sarcopenia correlates with poor nutrition, which itself predicts worse outcomes, increased complications, reduced quality of life, and, consequently, increased mortality. Factors including lack of exercise, malnutrition, hormone and cytokine imbalances, and developmental influences may also play a role in the development of sarcopenia.[70]

Notably, subgroup analysis found that although sarcopenia was associated with poorer OS in chemoradiotherapy versus surgery, this did not reach statistical significance. These results suggest that sarcopenia is predictive of mortality in patients with HNC independent of treatment modality. We would like to highlight that possibly, the effect of sarcopenia on the chemoradiotherapy subgroup is underestimated as patients would likely have been selected against chemotherapy if they were deemed medically unfit to begin with, as evidenced by poor Eastern Cooperative Oncology Group and/or Glasgow scores, at multidisciplinary tumor board discussions.[71,72] As such, the observed association between sarcopenia and chemoradiotherapy toxicity could have been underestimated in this analysis. Sarcopenia likely confers worse than observed survival in systemic treatment, and this phenomenon may be explained by the different indications for each treatment modality. Monotherapy with surgery or radiotherapy is commonly used for early cancers, while surgery with adjuvant chemoradiotherapy is typically reserved for locoregionally advanced cancers. It is reasonable to extrapolate that patients undergoing chemoradiotherapy may be more likely to be of an advanced stage of cancer compared with those undergoing surgery or radiotherapy only, except in selected indications such as organ-preservation in HNCs, the discussion of which is beyond the scope of our study.[73] The results of this study support the need for future interventional studies and randomized trials on the impact of sarcopenia treatment on mortality in HNC patients.

Subgroup analysis by geographical region demonstrated no significant differences in the association between sarcopenia and OS between studies conducted in Asia, Europe, and North America. The significant association of sarcopenia on OS was also observed across different geographical regions. BMI is known to differ between ethnic groups, with Asian populations found to have a lower BMI than Caucasian populations, given the same level of body fat, age and sex.[74] A higher BMI has also been shown to correlate with a lower incidence of sarcopenia.[75] These findings therefore suggest that sarcopenia is independently predictive of OS, regardless of population differences in BMI. Interestingly, the meta-regression revealed that the association between sarcopenia and OS was weaker among studies with higher mean BMI. Similar results have been reported in the literature, demonstrating that a BMI lower than 22.5 kg/m^2 is associated with an increased risk of all-cause mortality across 24 cancer types, including HNC.[76] The effects of BMI on OS may also be related to cancer cachexia, a potential underlying mechanism of sarcopenia.

Meta-regression revealed that lower BMI was associated with poorer OS. Published data suggest that low BMI confers a survival disadvantage in patients with HNC, whereas being overweight up to a BMI of 30 kg/m^2 confers a survival advantage, under the phenomenon known as the obesity paradox.[77] Several factors may contribute to this phenomenon. Lower BMI may weaken the host immune system and hence blunt the host response to treatment, whereas higher BMI may mitigate chemotherapy toxicity and provide nutritional reserves to safeguard against pharyngeal muscle dysfunction, which may predispose to malnutrition. It is plausible that patients with lower BMI at presentation have lost

significant weight due to advanced disease, hence their poor outcomes are a consequence of aggressive disease rather than low BMI alone.[78] The prevalence of low BMI increases with more advanced stages of oncological disease and studies have shown that such patients experience significant muscle loss before they appear cachectic.[79] Therefore, low BMI may be the late-stage manifestation of malnutrition, muscle loss, and poor physiological reserves. On the other hand, obesity is known to exacerbate sarcopenia by increasing infiltration of fat into muscle, lowering physical function, and increasing the risk of mortality, resulting in sarcopenic obesity.[80] Sarcopenic obesity has been found to be associated with worse oncological long-term outcomes in some cancers.[81,82] However, it is currently uncertain whether sarcopenic obesity confers a survival disadvantage in patients with HNC, and further studies may be useful in confirming this possible association. Taken together with the existing body of evidence, this meta-analysis supports current findings that BMI is a poor prognostic factor of OS in patients with HNC.

Interestingly, the meta-analysis of correlations demonstrated a statistically significant correlation between C3 CSA and SMI with their corresponding measurements at the L3 level. These results support those reported by Swartz et al., which showed that C3 muscle CSA strongly predicted L3 muscle CSA.[9] However, considerable debate surrounds the agreement between C3 CSA and L3 CSA, with subsequent studies finding weak agreement between C3 CSA and L3 CSA measurements, and C3 SMM and L3 SMM measurements.[49,53] It has been suggested that the results reported by Swartz et al. be attributed to the high proportion of non-sarcopenic subjects in their cohort, as their analyses was performed in a population including both HNC and trauma patients. Further high-quality studies may be useful to confirm the correlations between C3 and L3 muscle measurements.

There were appreciable limitations within this study. The majority of included studies utilized the Swartz prediction model for the conversion of C3 measures into predicted measures at L3.[9] This model was formulated from a small population of patients with HNCs, with an average BMI of 24 kg/m^2. Therefore, there are inherent limitations in the applicability of this model for the prediction of sarcopenia. Several included studies have used their own defined cut-off thresholds for sarcopenia using C3 measurements, such as C3 SMI. This reflects a current lack of consensus in the literature on how an acceptable C3 SMI measurement should be defined. Relatively high statistical heterogeneity was observed in the meta-analysis of prevalence of sarcopenia. There could have been incomplete adjustment or a lack of measurement for potential confounders. For instance, none of the included studies adjusted for nutrition or exercise status, which could have been a confounder of the association between sarcopenia and OS. There were also fewer studies that adjusted for tumor grade or aggressiveness compared with those that adjusted for tumor stage. Specific cancer sites and treatment modalities varied in the included studies, which may have added to the clinical heterogeneity of the included populations. To account for possible effect modifiers, the authors have therefore performed a subgroup analysis to stratify included studies by location of cancer and treatment modality.

CONCLUSION

This systematic review and meta-analysis of overall moderate quality of evidence found that CT-defined sarcopenia was associated with a significantly lower OS, DFS, DSS, and PFS, and increased chemotherapy or radiotherapy toxicity in patients with HNC. This association remained significant regardless of tumor stage, treatment modality, and geographical region, as demonstrated in subgroup analyses. Meta-regression found that higher BMI weakened the association between sarcopenia and OS. Our findings support the need for interventional studies and randomized trials to investigate sarcopenia as a potential modifiable risk factor for mortality in patients with HNCs. As the majority of patients undergoing treatment for HNCs would have a CT scan of the head and neck, where sarcopenia can be measured at the C3 vertebra, our findings are immediately applicable in routine clinical care.

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AUTHOR CONTRIBUTIONS Conceptualization: BYQT, LFT, AM. Data curation: JHK, CYJL, LTPT, EYXG. Formal analysis: JHK, CYJL LTPT. Supervision: BYQT, LFT, AM, JSYH, AJT. Writing – original draft: JHK, CYJL, LTPT. Writing – reviewing and editing: JHK, CYJL, LTPT, BKJT, EYXG, JSYH, AJT, AXS, AM, LFT, BYQT. All authors have read and approved the final version of this manuscript submitted for publication.

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