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SYSTEMATIC REVIEWS AND META-ANALYSES

Preoperative computed tomography-assessed sarcopenia as a predictor of complications and long-term prognosis in patients with colorectal cancer: a systematic review and meta-analysis

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Abstract

Background The relationship between computed tomography (CT)-assessed sarcopenia and colorectal cancer (CRC) prognosis varies in different studies. This systematic review aimed to examine the impact of preoperative CT-assessed sarcopenia on complications and long-term survival in CRC patients.

Methods The PubMed, Web of Science, Cochrane Library, and Embase databases were searched for relevant literature up to September 10, 2020. Data and characteristics for each study were extracted. Long-term outcomes were assessed using a comprehensive HR with a 95% CI. Complications were assessed using a comprehensive OR with 95% CI. The heterogeneity and publication bias were also investigated, and subgroup and sensitivity analyses were performed.

Results A total of 19 studies comprising 15,889 patients were included. The comprehensive results demonstrated that sarcopenia is significantly associated with overall survival of CRC patients (HR = 1.40, 95% CI = 1.25–1.58, $p < 0.001$). Patients with sarcopenia have a higher risk of complications compared to those without sarcopenia. In addition, sarcopenia is strongly associated with poor cancer-specific survival (HR = 1.49, 95% CI = 1.32–1.68, $p < 0.001$) and disease-free survival (HR = 1.59, 95% CI = 1.32–1.92, $p < 0.001$) in CRC patients. There is no significant relationship between sarcopenia and recurrence-free survival (HR = 1.32, 95% CI = 0.92–1.89, $p = 0.126$).

Conclusions Preoperative CT-assessed sarcopenia can be employed as an effective predictor of complications and long-term prognosis in CRC patients. Standardization of CT-assessed sarcopenia requires comprehensive consideration of race, muscle mass index, body mass index, and gender.

Keywords Colorectal cancer · Computed tomography-assessed sarcopenia · Complications · Prognosis · Meta-analysis

Introduction

Colorectal cancer (CRC) is one of the most common gastrointestinal cancers with a high incidence and mortality rate. CRC had a global estimated incidence of 1.8 million cases (10.2% of all new cases) and mortality of 861,000 cases (9.2% of all cancer deaths) in 2018 [1]. According to the latest 2020 statistics, CRC has become the second most common cancer and second leading cause of all cancer deaths in the USA [2]. Surgical treatment and radiochemotherapy are still the most effective means to improve the CRC patient survival rate. Recently, the rapid development of gene detection and biological targeting therapy has played a positive role in the treatment of CRC. However, short- and long-term outcomes in CRC patients are still unsatisfactory [3]. Therefore, it is necessary to carry out research on factors that may alter the prognostic stratification of CRC patients.

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At present, most studies focus on tumor pathology itself, while the influence of host-related factors on CRC patient prognosis is often ignored. Clinically, the Tumor Node Metastasis (TNM) classification of American Joint Committee on Cancer has been regarded as an important prognostic tool for CRC. However, tumor characteristics are not the only factor influencing prognosis. Many other factors, such as nutritional and immune status, also play an important role in tumor progression and are associated with patient prognosis. More and more studies in recent years have reported that host-related sarcopenia is a risk factor affecting the prognosis of various cancers, such as gastric [4], pancreatic [5], and lung [6] cancers. Sarcopenia is a syndrome characterized by progressive and systemic skeletal muscle mass loss [7]. Sarcopenia has been reported to be associated with numerous causes, such as insulin resistance, anabolic resistance, anorexia, and systemic inflammation [8, 9]. Muscle mass quantification by computed tomography (CT) is a broad and accurate method for assessing sarcopenia. At present, the most commonly used measurement method is to calculate the total skeletal muscle area (cm^2) at the level of the third lumbar vertebra, including the psoas muscle, lumbar muscle, erector spinae, transversus abdominis muscle, internal and external oblique muscles, and rectus abdominis, and the third lumbar vertebra skeletal mass index (L3SMI) by dividing by the height squared (m^2).

Patients with gastrointestinal tumors are commonly malnourished and are more prone to sarcopenia. This may be the result of the combined effects of malignant disease progression, host tumor response, anti-cancer treatment, and special comorbidities of gastrointestinal tumors (obstruction, bleeding, and perforation). Feliciano et al. conducted a study based on 2470 patients that showed that the combination of CT-assessed sarcopenia and inflammation indicators can effectively predict CRC patient prognosis [10]. Similarly, Dolan et al. proposed that CT-assessed sarcopenia is an important factor affecting long-term survival in CRC patients [11]. In addition, our previous studies confirmed that preoperative CT-assessed sarcopenia is an independent factor affecting complications and long-term prognosis in CRC patients, which can be used to assist the preoperative nutritional assessment of CRC patients [12, 13]. However, Vugt et al. believed that preoperative CT-assessed sarcopenia can be used to assess the risk of complications in CRC patients, but not to assess long-term efficacy [14]. Due to the heterogeneity of different studies, the role of CT-assessed sarcopenia in CRC patient outcomes in diverse populations remains controversial. Sun et al. [15] conducted a meta-analysis in 2018 to explore the prognostic value of CT-assessed sarcopenia in CRC patients. However, there were some limitations due to the small number of studies included. Moreover, many new studies on the relationship between CT-assessed sarcopenia and CRC have emerged in the past 2 years. Therefore, it is necessary to conduct the latest meta-analysis on the basis of existing evidence to investigate the value of preoperative CT-assessed sarcopenia in assessing complications and long-term prognosis in CRC patients.

Materials and methods

Data sources and search

This meta-analysis was strictly based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [16]. A systematic search was conducted on the value of preoperative CT-assessed sarcopenia in complications and long-term prognosis in CRC patients in the PubMed, Web of Science, Cochrane Library, and Embase databases using a combination of keywords and free words. The search was restricted to English-language publications up to September 10, 2020. The search terms were “sarcopenia”, “muscle depletion”, “muscle mass” AND “rectal neoplasms”, “colonic neoplasms”, “colon”, “rectum” AND “outcomes”, “survival”, “complications”, "comorbidity", and "prognosis". In addition, potential reviews and meta-analyses were manually examined to identify any other relevant literature that could be included in this study. The complete search strategy is detailed in the supplementary appendix.

Inclusion and exclusion criteria

The eligibility of each study was assessed based on the PICOS framework. Studies meeting the following criteria were included: (1) patients underwent CRC resection, and no other combined tumors and distant metastasis were present; (2) studies reported the prognostic value of preoperative CT-assessed sarcopenia on complications, overall survival (OS), cancer-specific survival (CSS), disease-free survival (DFS), and recurrence-free survival (RFS); (3) the dichotomy cut-off value for L3SMI was reported; (4) the HR and corresponding 95% CI were provided, or can be estimated from Kaplan–Meier survival curve; (5) the study design was limited to comparative studies (randomized controlled trials, case–control studies, retrospective studies, and prospective studies). Studies meeting the following criteria were excluded: (1) CRC patients with other combined tumors or metastases; (2) sarcopenia was not defined using preoperative CT-measured L3SMI; (3) insufficient data or no goal outcomes; (4) sample size < 100; (5) animal studies, reviews, conference abstracts, or letters. When studies were performed at the same center and during the same period, the study with the largest sample size was selected. OS was defined as the time from the diagnosis to death or last follow-up. CSS was defined as the time

from the diagnosis to death of CRC or last follow-up. DFS was defined as the time from radical surgery (when there is no tumor lesion in the body) to recurrence, metastasis, or death. RFS was defined as the time from removal of the lesion to recurrence or death.

Literature selection and data extraction

According to the established inclusion and exclusion criteria, two evaluators (H.X. and L.W.) independently screened the literature to select possible eligible studies. Any differences between evaluators were discussed with a third party until agreement was reached. The following information was extracted from each included study: general characteristics, including the first author's surname, year, country, study design, sample, age, gender ratio, analysis methods, and TNM stage; sarcopenia characteristics, including percent of sarcopenia, cut-off of male and female, sarcopenia prevalence, method, and definition; outcome, including primary (OS and complications) and secondary (CSS, DFS, and RFS) outcomes. The complication outcome in this study refers to total complications. The outcome evaluation of studies that only provided survival curves was completed using Engauge Digitizer v.4.1 software [17]. In addition, two independent evaluators used the Newcastle–Ottawa Scale (NOS) to evaluate the methodological quality of included studies. The NOS score ranged from 0 to 9, and a study with NOS score ≥ 6 was considered to be of high quality.

Statistical analysis

The comprehensive OR and 95% CI were used to evaluate the role of preoperative CT-assessed sarcopenia when assessing the risk of complications in CRC patients. The comprehensive HR and 95% CI were used to estimate the long-term prognostic effect of CT-assessed sarcopenia in CRC patients, including OS, CSS, DFS, and PFS. Heterogeneity between studies was tested using Higgins I^2 statistic and Cochran's Q test. If $I^2 \geq 50\%$ or $P_Q < 0.05$, the random effects model was used for statistical analysis. Otherwise, the fixed-effects model was utilized. To explore the source of potential heterogeneity, subgroup and meta-regression analyses were performed. Sensitivity analysis assessed study reliability by omitting one study at a time and examining the impact of each study on the comprehensive results. Potential publication bias was evaluated using Begg's and Egger's tests. If publication bias was present, the trim-and-fill method was used to further evaluate the stability of the results. A two-sided p value < 0.05 was considered significant. All statistical analyses were carried out using Stata 12.0 software (Stata Corp, College Station, TX, USA).

Results

Description of included studies

The PRISMA diagram for the study selection is represented in Fig. 1. According to the established search strategy, 1105 studies were initially evaluated, including 166 studies from PubMed, 430 from Web of Science, 137 from Cochrane Library, and 372 from Embase. After deleting duplicates and reviewing titles and abstracts, most of the irrelevant studies were excluded, leaving 53 to be further screened. After carefully reading the full text, 34 studies that did not meet the inclusion requirements were excluded. Ultimately, a total of 19 studies involving 15,889 cases were identified through systematic search [11, 18–35].

Study characteristics

Characteristics of the included studies are summarized in Table 1. These studies were published between 2015 and 2020, of which four were prospective comparative studies and 15 were retrospective comparative studies. Of these studies, ten were from Asia (five from China, three from Japan, and two from South Korea) and nine were from outside Asia (two from the UK, one from the USA, three from Canada, one from Finland, one from Sweden, and one from the Netherlands). The sample size median was 494, ranging from 142 to 3262. In addition, the NOS score for these 19 studies ranged from 6 to 8.

Assessment of sarcopenia prevalence

The description of sarcopenia from each study is presented in Table 2. In the present study, the median incidence of sarcopenia was 39.75%, ranging from 11.97 to 68.21%. Among Asian countries, the median prevalence of sarcopenia was 29.09%, ranging from 11.97 to 60.32%. The median prevalence was 43.19% in non-Asian countries, ranging from 27.48 to 59.77%.

Meta-analysis for OS

A total of 14 studies with 14,100 patients explored the prognostic value of CT-assessed sarcopenia for OS in CRC patients (Fig. 2). The comprehensive results showed that sarcopenia was significantly associated with OS in CRC patients (HR = 1.40, 95% CI = 1.25–1.58, $p < 0.001$). In other words, when compared to patients without sarcopenia, patients with sarcopenia have a worse OS. A random-effects model was used due to apparent heterogeneity ($I^2 = 54.3\%$, $P_Q = 0.008$). The sources of heterogeneity

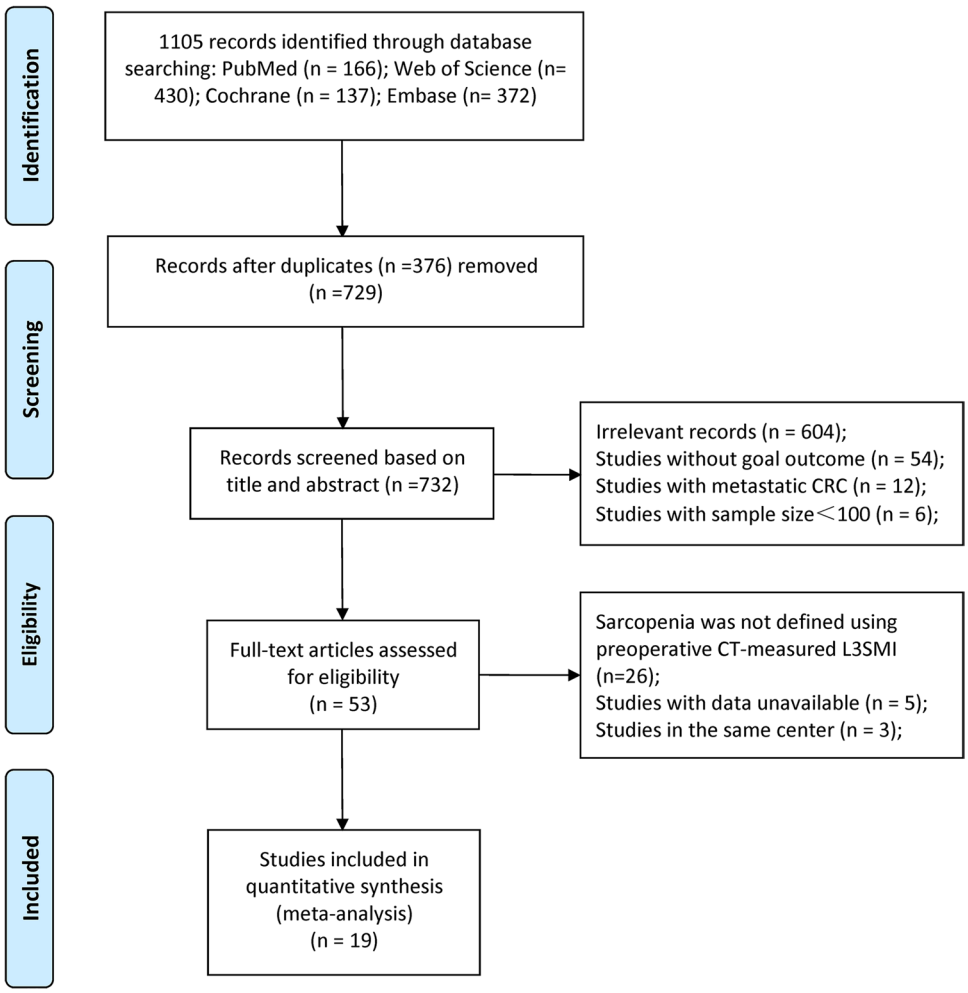

Fig. 1 Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram of study selection

were further analyzed based on study type, publication time, country, sample, sarcopenia criterion, and NOS score (Table 3). The results indicated that sarcopenia is an independent influencing factor for poor OS in each subgroup and there was no significant heterogeneity between the sample subgroup. Furthermore, meta-regression analysis indicated that the sample subgroup may be the source of potential heterogeneity ($P_{\text{design}} = 0.160$, $P_{\text{publication time}} = 0.349$, $P_{\text{country}} = 0.476$, $P_{\text{sample}} = 0.047$, $P_{\text{sarcopenia criterion}} = 0.667$, and $P_{\text{NOS score}} = 0.181$). Based on the subgroup and meta-regression analyses results, it was speculated that OS meta-analysis heterogeneity might be due to the different sample sizes of each study. In order to verify the stability of the present study, sensitivity analysis was conducted by removing one study at a time (Fig. 3). The results showed that removing any one study has little effect on the comprehensive results, indicating that the present results are reliable. In the analysis of publication bias, research using visual funnel plots was basically symmetrical without obvious publication bias in the Begg's ($p = 0.125$; Fig. 4a) and Egger's ($p = 0.115$; Fig. 4b) tests.

Meta-analysis for complications

The relationship between preoperative CT-assessed sarcopenia and complications was reported in six studies with 3419 cases (Fig. 5a). According to a fixed effects model ($I^2 = 50.0\%$, $P_Q = 0.075$), the combined results showed that sarcopenia was significantly associated with complications (OR = 1.82, 95% CI = 0.36–2.44, $p < 0.001$). Thus, patients with sarcopenia have a higher risk of complications compared to patients without sarcopenia. Subgroup analysis results further demonstrated that sarcopenia is an independent factor affecting complications in CRC patients independent of all subgroup factors (Table 4). In addition, sensitivity analysis was performed by removing each included study one at a time (Fig. 6a). The results showed that ignoring any included study does not change the comprehensive effect of sarcopenia on complications. Since a large asymmetry is observed in the funnel plot and Begg's ($p = 0.009$; Fig. 7a) and Egger's ($p < 0.001$; Fig. 7c) tests are both < 0.05, a potential publication bias is implied. Three estimation studies were supplemented with the trim-and-fill

Table 1 Characteristics of included studies

Research	Year	Country	Study design	Sample	Age (years)	Gender ratio	Follow-up (months)	Analysis	Stage	Outcome	NOS
Huang et al	2015	China	Prospective	142	Mean 62.03 ± 12.58	88/54	NA	M	I–III	Complications	7
Miyamoto et al	2015	Japan	Retrospective	220	Median 70 (30–93)	135/85	> 60	M	I–III	OS, RFS, CSS	7
Malietzis al	2016	UK	Retrospective	805	Median 69 (61–77)	472/333	Median 47 (24.9–65.6)	M	I–IV	OS, DFS	6
Caan et al	2017	Canada	Retrospective	3262	NA	1634/1628	Median 69.6 (0.0–118.8)	M	I–III	OS, CSS	6
Feliciano et al	2017	USA	Retrospective	2470	NA	1251/1219	NA	M	I–III	OS, CSS	6
Chen et al	2018	China	Prospective	376	Mean 64.33 ± 12.3	209/94	NA	M	I–IV	Complications	7
Nakanishi et al	2018	Japan	Retrospective	494	Mean 66.1 ± 12.4	298/196	Median 43.6	M	I–IV	Complications	8
Sueda et al	2018	Japan	Retrospective	211	NA	134/77	NA	M	I–IV	OS, CSS, DFS	7
Vugt et al	2018	Netherlands	Prospective	816	NA	440/376	Median 76.5	M	I–III	OS, CSS, DFS	7
Dolan et al	2018	UK	Prospective	650	Mean 70.6 ± 5.4	354/296	Median 44 (1–110)	M	I–III	OS	6
Hopkins et al	2019	Canada	Retrospective	968	Mean 65.8 ± 11.8	589/379	Median 62.4 (0.12–123)	M	I–III	OS, RFS, CSS	6
Yang et al	2019	China	Retrospective	417	Mean 57.9 ± 11.3	251/166	NA	M	I–III	Complications	7
Aro et al	2020	Finland	Retrospective	348	Mean 68 ± 11.5	182/166	Mean 72	M	I–III	OS	6
Chen et al	2020	China	Retrospective	360	Mean 72 ± 11.0	214/146	NA	M	I–IV	Complications	7
Han et al	2020	Korea	Retrospective	1384	Mean 59.0 ± 10.9	888/496	> 60	U and M	I–III	OS, RFS	6
Lee et al	2020	Korea	Retrospective	214	NA	126/90	Median 54 (2–137)	M	II–III	OS, DFS	7
Shirdel et al	2020	Sweden	Retrospective	722	NA	NA	Median 74.4 (56.4–130.8)	M	I–III	OS, CSS	6
Xiao et al	2020	Canada	Retrospective	1630	Mean 64.0 ± 11.3	724/906	Median 72 (0–118.8)	M	I–III	Complications, OS	7
Wang et al	2020	China	Retrospective	400	Mean 57.80 ± 13.09	257/143	Median 63 (6–80)	M	I–III	OS, DFS	7

Table 2 Definition and cut-off values of sarcopenia measured by the third lumbar vertebra skeletal muscle index (L3SMI) in our included studies

Research	Sarcopenia (%)	Cut-off (male)	Cut-off (female)	Method	Sarcopenia criterion
Huang et al	11.97	36.00	29.00	Cut-off from Iritani et al	Male: < 36 cm^2/m^2, handgrip strength < 26 kg, 6 m usual gait speed < 0.8 m/s; female: < 29 cm^2/m^2, handgrip strength < 18 kg, 6 m usual gait speed < 0.8 m/s
Miyamoto et al	25.00	49.50	42.10	Cut-off from the third quartile	Male: < 49.5 cm^2/m^2; female: < 42.1 cm^2/m^2
Malietzis et al	39.75	52.40	38.50	Cut-off from Prado et al.	Male: < 52.4 cm^2/m^2; female: < 38.5 cm^2/m^2
Caan et al	42.40	52.30/54.30	38.60/46.60	Cut-off from Caan et al	Male: < 52.3 cm^2/m^2 (BMI < 30 kg/m^2) or < 54.3 cm^2/m^2 (BMI ≥ 30 kg/m^2); female: < 38.6 cm^2/m^2 (BMI < 30 kg/m^2) or < 46.6 cm^2/m^2 (BMI ≥ 30 kg/m^2)
Feliciano et al	45.87	52.00/54.00	38.00/47.00	Cut-off from Caan et al	Male: < 52 cm^2/m^2 (BMI < 30 kg/m^2) or < 54 cm^2/m^2 (BMI ≥ 30 kg/m^2); female: < 38 cm^2/m^2(BMI < 30 kg/m^2) or < 47 cm^2/m^2 (BMI ≥ 30 kg/m^2)
Chen et al	24.47	40.80	34.90	Cut-off from Zhuang et al	Male: < 40.8 cm^2/m^2, handgrip strength < 26 kg, 6 m usual gait speed < 0.8 m/s; female: < 34.9 cm^2/m^2, handgrip strength < 18 kg, 6 m usual gait speed < 0.8 m/s
Nakanishi et al	60.32	52.40	38.50	Cut-off from Prado et al.	Male: < 52.4 cm^2/m^2; female: < 38.5 cm^2/m^2
Sueda et al	49.76	43.00/53.00	41.00	Cut-off from Martin et al	Male: < 43 cm^2/m^2 (BMI < 25 kg/m^2) or < 53 cm^2/m^2 (BMI > 25 kg/m^2); female: < 41 cm^2/m^2
Vugt et al	50.37	43.00/53.00	41.00	Cut-off from Martin et al	Male: < 43 cm^2/m^2 (BMI < 25 kg/m^2) or < 53 cm^2/m^2 (BMI > 25 kg/m^2); female: < 41 cm^2/m^2
Dolan et al	43.54	43.00/53.00	41.00	Cut-off from Martin et al	Male: < 43 cm^2/m^2 (BMI < 25 kg/m^2) or < 53 cm^2/m^2 (BMI > 25 kg/m^2); female: < 41 cm^2/m^2
Hopkins et al	27.48	45.70/47.10	31.60/38.50	Cut-off from overall survival	Male: < 45.7 cm^2/m^2 (BMI < 25 kg/m^2) or < 47.1 cm^2/m^2 (BMI ≥ 25 kg/m^2); female: < 31.6 cm^2/m^2 (BMI < 25 kg/m^2) or < 38.5 cm^2/m^2 (BMI ≥ 25 kg/m^2)
Yang et al	14.63	52.40	38.90	Cut-off from International Consensus	Male: SMI < 52.4 cm^2/m^2; female: SMI < 38.9 cm^2/m^2
Aro et al	59.77	43.00/53.00	41.00	Cut-off from Martin et al	Male: < 43 cm^2/m^2 (BMI < 25 kg/m^2) or < 53 cm^2/m^2 (BMI > 25 kg/m^2); female: < 41 cm^2/m^2
Chen et al	36.94	40.80	34.90	Cut-off from Zhuang et al	Male: < 40.8 cm^2/m^2, handgrip strength < 26 kg, 6 m usual gait speed < 0.8 m/s; female: < 34.9 cm^2/m^2, handgrip strength < 18 kg, 6 m usual gait speed < 0.8 m/s
Han et al	68.21	52.40	38.50	Cut-off from Prado et al	Male: SMI < 52.4 cm^2/m^2; female: SMI < 38.5 cm^2/m^2
Lee et al	33.18	46.40	37.50	Cut-off from Takagi et al	Male: SMI < 46.4 cm^2/m^2; female: SMI < 37.5 cm^2/m^2
Shirdel et al	31.99	46.00	30.80	Cut-off from the third quartile	Male: SMI < 46.0 cm^2/m^2; female: SMI < 30.8 cm^2/m^2

Table 2 (continued)

Research	Sarcopenia (%)	Cut-off (male)	Cut-off (female)	Method	Sarcopenia criterion
Xiao et al	43.19	52.30/54.30	38.60/46.60	Cut-off from Caan et al	Male: < 52.3 cm^2/m^2 (BMI < 30 kg/m^2) or < 54.3 cm^2/m^2 (BMI ≥ 30 kg/m^2); female: < 38.6 cm^2/m^2 (BMI < 30 kg/m^2) or < 46.6 cm^2/m^2 (BMI ≥ 30 kg/m^2)
Wang et al	24.75	38.89	33.28	Cut-off from the quartiles	Male: SMI < 38.89 cm^2/m^2; Female: SMI < 33.28 cm^2/m^2

method, resulting in a symmetric funnel plot (Fig. 7b) with an adjusted OR = 1.47 and 95% CI = 1.09–1.99 ($p = 0.012$), suggesting that correcting potential publication bias does not alter the significant association of sarcopenia with complications.

Meta-analysis for CSS/DFS/RFS

The present study also investigated the effect of CT-assessed sarcopenia on CSS/DFS/RFS prognosis in CRC patients. Seven studies comprising 8669 patients reported the prognostic value of sarcopenia for CSS (Fig. 5b). Comprehensive results suggested that sarcopenia is strongly associated with poor CSS in CRC patients (HR = 1.49, 95% CI = 1.32–1.68, $p < 0.001$). A fixed-effects model was used to assess heterogeneity ($I^2 = 0.0\%$, $P_Q = 0.705$). Five studies involving 2446 patients examined the relationship between sarcopenia and DFS (Fig. 5c). Since no heterogeneity was present, the fixed-effects model was adopted ($I^2 = 46.4\%$, $P_Q = 0.114$). The comprehensive results showed that sarcopenia patients had poorer DFS when compared to patients without sarcopenia (HR = 1.59, 95% CI = 1.32–1.92, $p < 0.001$). However, the comprehensive results from three studies involving 2572 patients suggested that sarcopenia is not an independent factor for adverse RFS in CRC patients (HR = 1.32, 95% CI = 0.92–1.89, $p = 0.126$; Fig. 5d). Sensitivity analysis showed that omitting any included studies did not change the outcome of sarcopenia's comprehensive meta-analysis for CSS (Fig. 6b), DFS (Fig. 6c), and RFS (Fig. 6d), suggesting that the present findings are reliable.

Discussion

There is growing evidence that various changes occur in the body composition of cancer patients, including muscle, fat, and bone. Therefore, body composition has become an increasingly important prognostic factor for cancer patients [36]. In recent years, it has been observed that sarcopenia is a common pathological body composition change in cancer

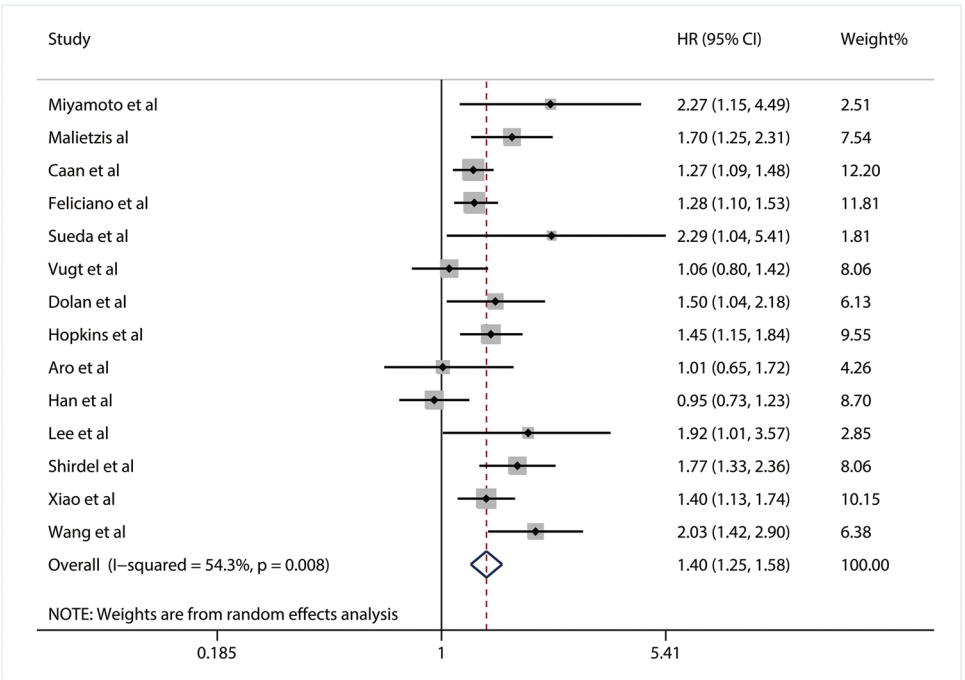

Fig. 2 Forest plot for the association between sarcopenia and overall survival

Table 3 Stratification analysis of the meta-analysis for overall survival

Subgroup	No. of studies	No. of patients	Pooled HR (95% CI)	*p* value	Heterogeneity	
					I^2 (%)	P_Q
Altogether	14	14,100	1.40 (1.25–1.58)	< 0.001	54.3	0.008
Study type						
Retrospective	12	12,634	1.43 (1.26–1.63)	< 0.001	56.4	0.008
Prospective	2	1466	1.24 (0.88–1.73)	0.220	52.7	0.146
Publication time						
< 2019	7	8434	1.36 (1.19–1.57)	< 0.001	38.9	0.132
≥ 2019	7	5666	1.43 (1.16–1.75)	0.001	66.6	0.006
Country						
Asian	5	2429	1.71 (1.09–2.67)	0.019	76.3	0.002
Non-Asian	9	11,671	1.36 (1.23–1.50)	< 0.001	30.3	0.176
Sample						
< 800	7	2765	1.70 (1.42–2.05)	< 0.001	16.6	0.303
≥ 800	7	11,335	1.28 (1.14–1.44)	< 0.001	48.8	0.069
Sarcopenia criterion						
Only SMI	7	7007	1.54 (1.23–1.93)	< 0.001	71.6	0.002
SMI and BMI	7	7093	1.32 (1.18–1.47)	< 0.001	9.3	0.358
NOS score						
6	8	10,609	1.34 (1.17–1.53)	< 0.001	54.4	0.032
7	6	3491	1.60 (1.23–2.07)	< 0.001	57.2	0.040

patients, which has gradually attracted more and more attention. Sarcopenia was first proposed by Rosenberg et al. in 1989 as an evaluation of skeletal muscle degeneration in the elderly [37]. Recently, sarcopenia has been found to be an adverse factor affecting postoperative complications and long-term prognosis of many malignancies [38, 39]. Currently, there are many methods for assessing sarcopenia, including CT, magnetic resonance imaging, and dual energy X-ray absorptiometry. However, the recent study by Simonsen et al. showed that the incidence of sarcopenia defined

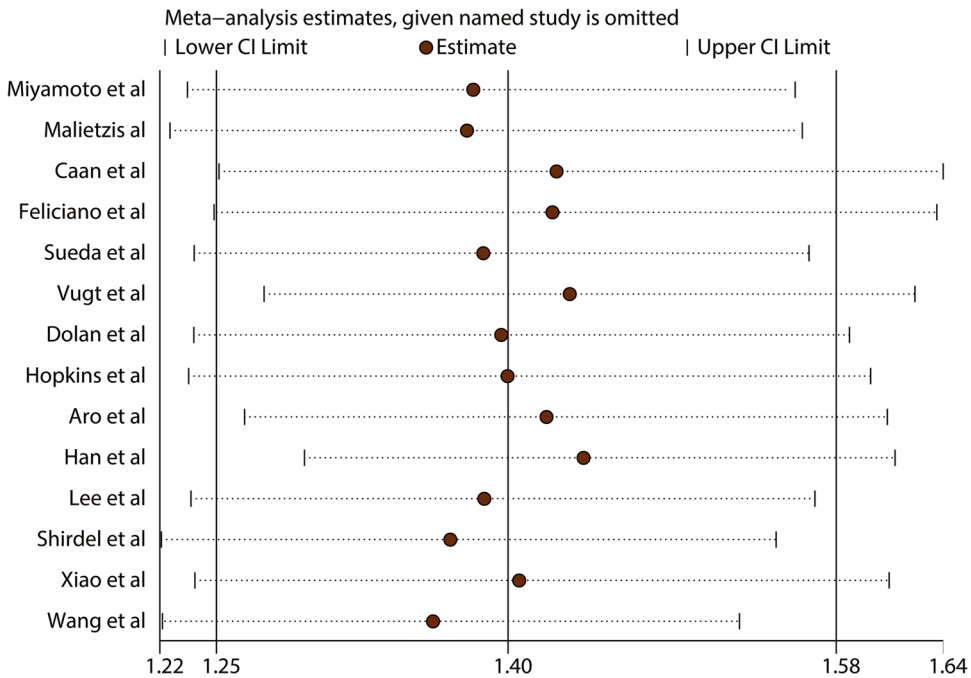

Fig. 3 Sensitivity analysis for the association between sarcopenia and overall survival

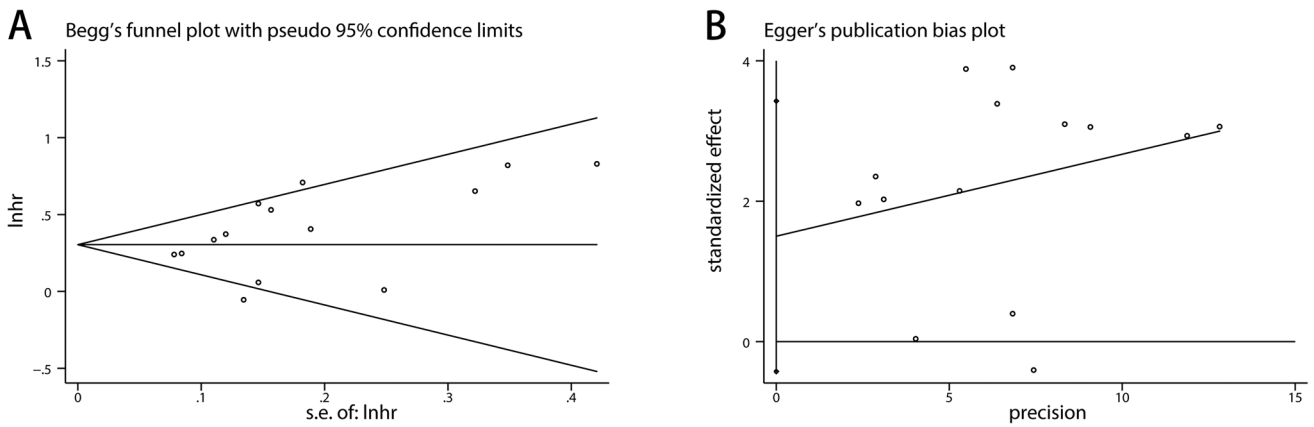

Fig. 4 Plots for publication bias in meta-analysis for overall survival. **a** Begg's funnel plot; **b** Egger's publication bias plot

by different methods varies greatly and is less consistent [40]. CT is considered the gold standard for muscle mass measurement because it can provide important quantitative information about muscle composition and distribution [41, 42]. In addition, routine use of CT imaging in preoperative evaluation of CRC patients provides an easily available and cost-free resource for sarcopenia identification.

This systematic review discussed the prognostic implications of CT-assessed sarcopenia in CRC patients by including 19 studies involving 15,889 cases. The results suggested that CT-assessed sarcopenia is an important independent risk factor for OS in CRC patients. Subgroup and meta-regression analyses showed that the reason for the heterogeneity in the comprehensive results may be explained by different sample sizes in each study (sample sizes ranged from 142 to 3262). Despite the heterogeneity, sensitivity analysis results still suggested that the present research is trustworthy. In addition, sarcopenia may increase the risk of total complications by 1.36–2.44-fold in CRC patients, which may be due to the fact that sarcopenia patients may

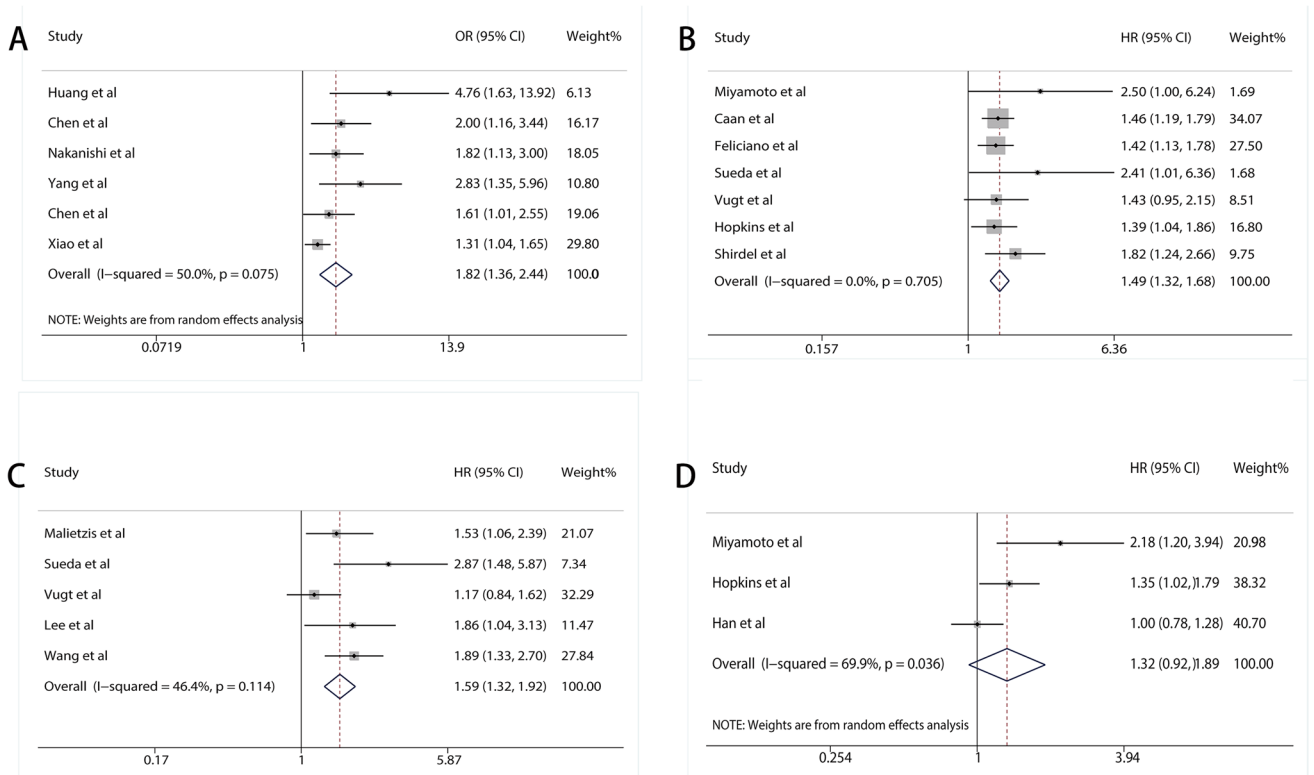

Fig. 5 Forest plot for the correlation of sarcopenia with complication (**a**)/CSS (**b**)/DFS (**c**)/RFS (**d**)

Table 4 Stratification analysis of the meta-analysis for postoperative complications

Subgroup	No. of studies	No. of patients	Pooled HR (95% CI)	*p* value	Heterogeneity	
					I^2 (%)	P_h
Altogether	6	3419	1.82 (1.36–2.44)	< 0.001	50	0.075
Study type						
Retrospective	4	2901	1.60 (1.22–2.11)	0.001	37.6	0.187
Prospective	2	518	2.71 (1.21–6.10)	0.016	49.9	0.158
Publication time						
< 2019	3	1012	2.14 (1.43–3.23)	< 0.001	22.8	0.274
≥ 2019	3	2407	1.59 (1.11–2.28)	0.011	50.4	0.133
Country						
Asian	5	1789	2.01 (1.53–2.64)	< 0.001	8.1	0.36
Non-Asian	1	1630	1.31 (1.04–1.65)	0.022	NA	NA
Sample						
< 800	5	1789	2.01 (1.53–2.64)	< 0.001	8.1	0.36
≥ 800	1	1630	1.31 (1.04–1.65)	0.022	NA	NA
Sarcopenia criterion						
Only SMI	2	911	2.08 (1.38–3.13)	0.002	0	0.33
SMI and BMI	1	1630	1.31 (1.04–1.65)	0.022	NA	NA
SMI + strength + function	3	878	2.07 (1.30–3.29)	0.002	40.1	0.188
NOS						
7	5	2925	1.88 (1.31–2.69)	0.001	58.5	0.047
8	1	494	1.82 (1.12–2.97)	0.016	NA	NA

feel weak, have limited mobility, and have greater difficulty recovering from major surgical trauma, thereby affecting the postoperative recovery process and leading to the occurrence of adverse complications. The consistent sensitivity and subgroup analyses results showed that our results are reliable and robust. Although publication bias was detected, it was modified using trim-and-fill method, and there was no significant change in the merged results, indicating that our conclusions were reliable. Moreover, sarcopenia was also associated with poor CSS and DFS in CRC patients. In summary, CT-assessed sarcopenia is an effective predictor of short- and long-term prognosis in CRC patients.

Studies have shown that sarcopenia is most likely to operate through physiological and metabolic pathways (such as systemic inflammatory response) as well as behavioral pathways (such as reduced physical activity due to dehydration and fatigue). Systemic inflammatory response plays a major role in the occurrence and development of sarcopenia [43]. Dodson et al. suggested that sarcopenia may be associated with increased metabolic activity in tumor patients, which leads to systemic inflammation and muscle wasting [44]. Richards et al. demonstrated a significant correlation between sarcopenia and systemic inflammatory response [45]. In addition, studies have suggested that inflammatory cytokines may be involved in sarcopenia by interfering with insulin-like growth factor-I signaling in skeletal muscle [46]. CRC patients often suffer from malnutrition, weight loss, and sarcopenia. This not only increases hospitalization time and costs, but also affects patient quality of life and survival. Studies have demonstrated that endurance and resistance training for cancer patients can effectively improve or maintain the quality and function of skeletal muscle [47, 48]. A high-protein diet and certain nutritional supplements (melanocortin-4 receptor antagonists and IL-6 antagonists) can increase or prevent further loss of muscle mass [49, 50]. Therefore, early nutritional support therapy and muscle mass maintenance exercise may help to improve the outcome in sarcopenia patients during treatment.

At present, there is no uniform standard for the diagnosis of CT-assessed sarcopenia. The diagnostic rate of sarcopenia largely depends on how to determine the diagnostic threshold. In our systematic review, 11 criteria were used to define sarcopenia. When Western standards (Prado et al. and Martin et al.) were applied in the Asian population, the diagnostic rate of sarcopenia was consistently higher than that of some Asian standards (Zhuang et al. and Iritani et al.). There are differences in body composition and muscle mass among different races. Studies have demonstrated that Asians have significantly lower muscle mass than Westerners by about 17% [51]. The mixed use of diagnostic criteria based on different races may lead to research heterogeneity. In addition,

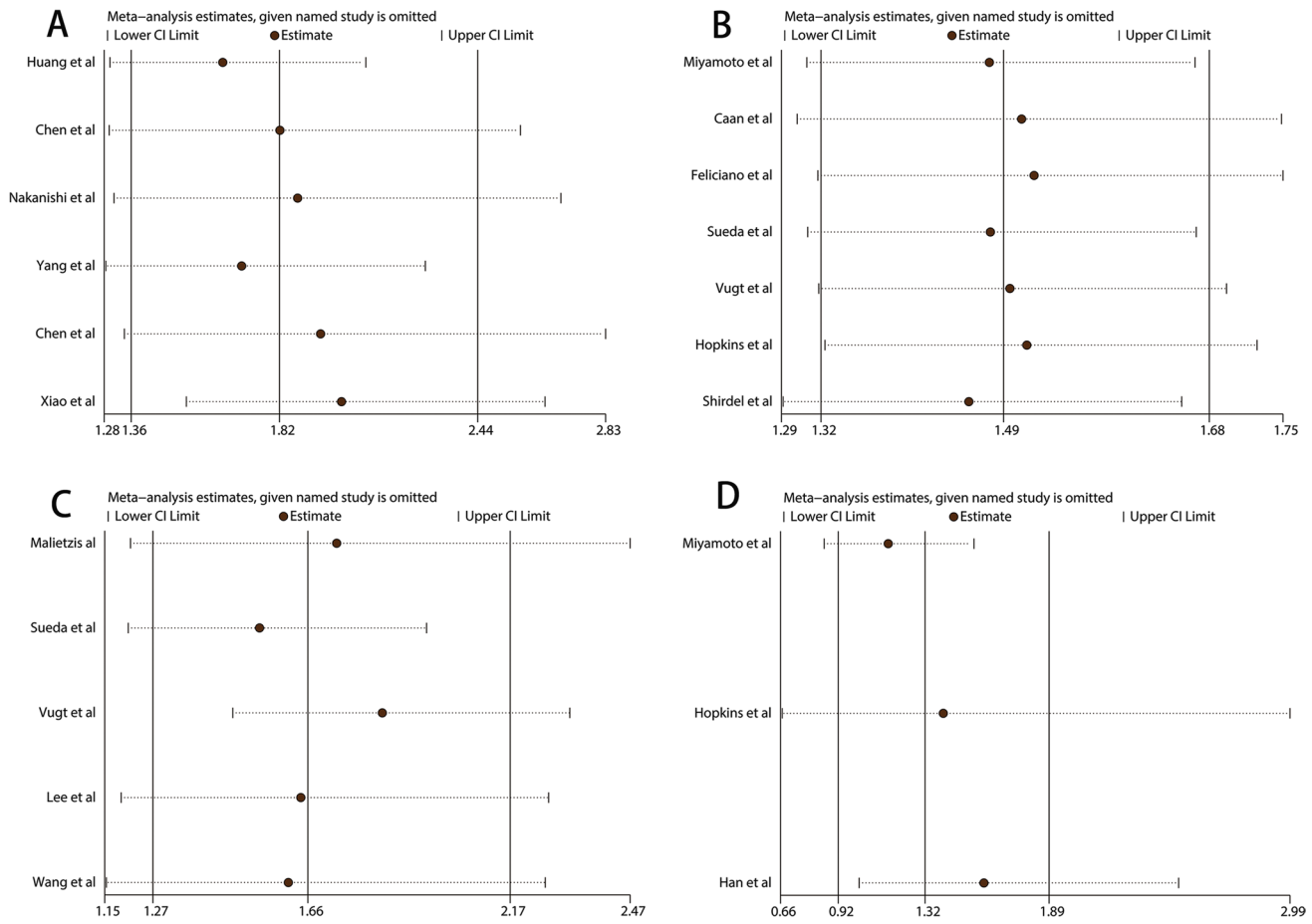

Fig. 6 Sensitivity analysis for the correlation of sarcopenia with complication (**a**)/CSS (**b**)/DFS (**c**)/RFS (**d**). CSS, cancer-specific survival; DFS, disease-free survival; RFS, recurrence-free survival

studies combining muscle mass and body mass indices as criteria for sarcopenia had less fluctuation in the diagnostic rate of sarcopenia than studies using muscle mass index alone, suggesting that a combination of muscle mass and body mass indices may help to reduce heterogeneity and standardize the criteria for sarcopenia. Gender is also one of the main factors that affect the diagnostic criteria for sarcopenia. The different physique of male and female often cause the threshold of sarcopenia in male to be higher than that in female. In this study, the difference in sarcopenia thresholds between male and female ranged from 2 to 15.2 (median of 12). Based on current evidence,

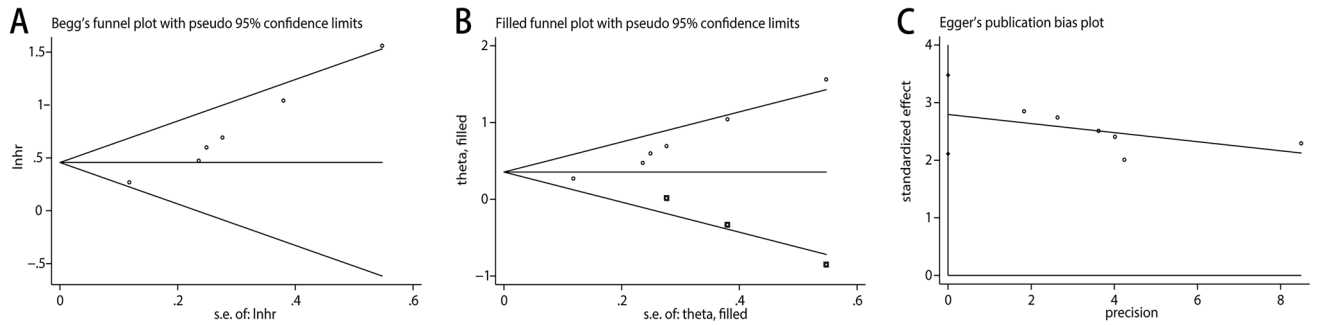

Fig. 7 Plots for publication bias test in meta-analysis for complication. **a** Begg's funnel plot; **b** the trim-and-fill methods; **c** Egger's publication bias plot

standardized sarcopenia should be considered in terms of race, muscle mass index, body mass index, and gender. Our meta-analysis demonstrated that CT-assessed sarcopenia is an effective predictor of poor outcomes for CRC patients. Early nutritional intervention may help improve the prognosis of these sarcopenia patients. Therefore, the development of standardized sarcopenia is conducive to more accurate and convenient identification of patients with poor prognosis in sarcopenia state, thereby timely intervention can be conducted to improve the prognosis of these patients.

Some study limitations still need to be resolved. First, there was significant heterogeneity in the analysis of the relationship between sarcopenia and OS. However, sensitivity analysis identified no significant change in the prognostic impact of sarcopenia on OS meta-analysis. Based on the subgroup and meta-regression analyses results, it was speculated that heterogeneity may be caused by the large difference in sample size among studies. Second, publication bias was present in the meta-analysis for complications. However, there were no significant differences between the results before and after the application of the trim-and-fill method, suggesting that publication bias did not change the significant correlation between sarcopenia and complications. In summary, despite these limitations, the present results provide valuable support for assessing the prognostic value of CT-assessed sarcopenia in CRC patients.

Conclusions

This study suggested that preoperative CT-assessed sarcopenia can be employed as an effective predictor of complications and OS/CSS/DFS in CRC patients. Early identification of preoperative sarcopenia and timely administration of nutritional intervention and exercise training may help to improve the adverse outcomes in CRC patients. In addition, the prevalence of sarcopenia correlates with the L3SMI threshold and standardization of CT-assessed sarcopenia requires comprehensive consideration of race, muscle mass index, body mass index, and gender.

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Author's contributions J.L.G., S.Y.T., H.L.X., and L.S.W. designed this research; M.X.L., G.H.Y., and S.Y.T. performed the statistical analysis; H.L.X. and L.S.W. performed the data extraction, and drafted and revised the manuscript. All authors reviewed and approved the final manuscript.

Data availability All datasets presented in this study are included in the article.

Declarations

Ethical approval This article did not contain any studies with human participants or animals performed by any of the authors.

Informed consent Considering the nature of this study, informed consent was not required.

Conflict of interest The authors declare no competing interests.

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Research registration number

The protocol was registered at PROSPERO: CRD42020216306.