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ORIGINAL ARTICLE

Can sarcopenia be a predictor of prognosis for patients with non-metastatic colorectal cancer? A systematic review and meta-analysis

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Abstract

Purpose We aimed to explore whether sarcopenia diagnosed with the third lumbar vertebra skeletal muscle index (L3 SMI) can be a predictor of prognosis for colorectal cancer (CRC) patients.

Methods A systematic review and meta-analysis was conducted using PubMed, Embase, and the Web of Science databases. All original comparative studies published in English that were related to sarcopenia versus non-sarcopenia in non-metastatic CRC patients based on postoperative and survival outcomes were included. Data synthesis and statistical analysis were carried out using Stata software.

Results A total of 12 studies including 5337 patients were included in our meta-analysis. In our overall analyses of postoperative outcomes, we indicated that CRC patients with sarcopenia would have longer hospital stays, higher incidence of total postoperative morbidity (OR = 1.70, 95% CI = 1.07–2.70, $P < 0.01$), mortality (OR = 3.45, 95% CI = 1.69–7.02, $P < 0.01$), and infection (OR = 2.21, 95% CI = 1.50–3.25, $P < 0.01$) but not anastomosis leakage or intestinal obstruction when compared to non-sarcopenia patients. Regarding survival outcomes, our results showed that sarcopenia predicted a decreased overall survival (HR = 1.63, 95% CI = 1.24–2.14, $P < 0.01$), disease-free survival, and cancer-specific survival for non-metastatic CRC patients. Moreover, our subgroup analyses showed similar tendency with our overall analyzed results.

Conclusions Sarcopenia diagnosed with L3 SMI can be a negative predictor of postoperative and survival outcomes for non-metastatic CRC patients. Prospective studies with a uniform definition of sarcopenia are needed to update our findings.

Keywords Sarcopenia · Colorectal cancer · Skeletal muscle mass · Meta-analysis

Introduction

Colorectal cancer (CRC) is one of the most common types of cancer worldwide with high morbidity and mortality [1]. Although surgical resection remains as the main treatment for non-metastatic CRC patients, approximately 20–30% patients may still suffer from postoperative complications such as surgical site infection, anastomosis leakage, or intestinal obstruction [2–5]. Meanwhile, prognostic stratification of patients is usually guided by tumor pathology after potentially curative surgery; however, long-term survival outcomes can also be negatively impacted by postoperative complications and baseline host-related factors [4, 6–9]. Therefore, exploring host-related factors, which can predict the prognosis of postoperative and survival outcomes, are very important to identify the subgroup population that can benefit more from colorectal resection.

Body composition is a common host-related factor, and there is mounting evidence that indicates that patients with cancer undergo a variety of changes in body composition that alters their portion of muscle, fat, and bone [10]. Notably, sarcopenia is a syndrome characterized by progressive and generalized loss of skeletal muscle mass (SMI) [11]. To date, according to the consensuses of the European Working Group on Sarcopenia in Older People (EWGSOP) and the Asian Working Group for Sarcopenia (AWGS), muscle strength and physical performance are also important components of sarcopenia [12, 13]. However, there is still no uniform

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standard to measure and define sarcopenia to date [14]. The most common method in measuring SMI is using preoperative computerized tomography (CT) scan at the third lumbar vertebra (L3) [15], which is commonly used in retrospective studies to measure SMI and to define sarcopenia. Growing evidence indicates that patients with sarcopenia have a negative prognosis of postoperative or survival outcomes in various types of tumors, such as gastric, pancreatic, or lung cancer [16–19]. However, the impact of sarcopenia in patients with non-metastatic CRC remains controversial. Hence, it is urgent to provide comprehensive evidence to evaluate the impact of sarcopenia in CRC patients.

Based on the aforementioned, we aimed to explore whether sarcopenia diagnosed with L3 SMI can be a negative prognostic predictor in terms of postoperative and survival outcomes for patients with non-metastatic CRC.

Methods

Search strategy

Based on the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) (http://www.prisma-statement.org/), we conducted our systematic review and meta-analysis. Our search was restricted to the English language based on the following MeSH/main keywords: "colorectal," "rectal," "colonic," "colon," "rectum," "sarcopenia," "myopenia," and "muscle mass" using datasets from PubMed, Embase, and Web of Science (up to April 4, 2018). To avoid redundant studies, we checked all authors and organizations and evaluated the recruitment period and population of patients enrolled in each study. In addition, the lists of references in the relevant studies were also screened for additional studies.

Inclusion and exclusion criteria

According to the PICOS criteria (population, intervention, comparison, outcomes, and study design), studies were selected in our present meta-analysis according to the following eligibility criteria: (1) population: patients with primary colorectal cancer without metastases; (2) intervention: sarcopenia diagnosed by preoperative CT scan with L3SMI and underwent colorectal resection; (3) comparison: sarcopenia versus non-sarcopenia colorectal cancer patients; (4) outcomes: postoperative (hospital stay, total postoperative complications, postoperative mortality, anastomosis leak, infection, intestinal obstruction), and survival outcomes (OS, DFS and CSS) compared between the two groups; and (5) study design: comparative studies (retrospective and prospective studies). In addition, the exclusion criteria were (1) patients with other cancer types or metastases; (2) sarcopenia diagnosed by other methods; and (3) studies with insufficient data or absence of the outcomes of interest.

Data extraction and quality assessment of included studies

Two reviewers (GuangweiSun and Yalun Li) reviewed and assessed each of the included studies independently, and the following information was collected: first author, year of publication, country, study type, number of patients enrolled, age, body mass index (BMI), male/female percentage, and cutoff value of L3SMI. In addition, data extraction of postoperative and survival outcomes (OS was defined as event of death due to any cause; DFS was defined as event of disease recurrence or death; and CSS was defined as event of death due to cancer) was also performed by the two reviewers independently. Moreover, the Newcastle–Ottawa Scale (NOS) criterion was used to evaluate the quality of the studies included [20]. All disagreements in terms of the aforementioned studies were resolved by discussion between the two reviewers (GuangweiSun and Yalun Li).

Statistical analysis

In our systematic review and meta-analysis, continuous variables were analyzed by the weighted mean difference (WMD), and dichotomous variables were analyzed by the odds ratios (ORs). If the study did not provide values for the mean and standard deviation (SD), we used the method of Hozo et al. to calculate the mean and SD for analyses [21]. Meanwhile, the most appropriate statistic to use for evaluating survival outcomes (time-to-event outcomes) was the hazard ratio (HR). If studies did not provide the HR directly, we obtained an estimated HR by methods designed by Tierney [22]. All analyses were performed using Stata software, version 12.0 (2011; Stata Corp., College Station, TX, USA). All the analyses in this study used a random-effects model because it provided more conservative estimates and was tailored to multicenter studies in which heterogeneity was usually present [23]. All statistical values were reported with the 95% confidence interval (CI) and a two-tailed P value less than 0.05 was defined as statistical significance. Subgroup analyses were conducted in terms of study type, total patients number, NOS scores, country, and cutoff values of sarcopenia based on OS and total postoperative complications. Finally, publication bias was assessed using Begg's and Egger's tests [24, 25].

Results

Selected studies

Based on our search strategy, a total of 376 published studies were identified. After removing the duplicates, screening the

title and abstract, and further evaluating, finally, 12 comparative studies were included in the systematic review and meta-analysis [11, 26–36]. A flow chart of the search strategies, which includes the reasons for exclusion of studies, is illustrated in Fig. 1. Among the included studies, five studies were prospective comparative studies [26, 29, 30, 33, 36], and the other seven were designed retrospectively [11, 27, 28, 31, 32, 34, 35]. In addition, six studies were conducted in Asian countries [26, 27, 29, 31, 32, 35], the other six studies were from non-Asian countries [11, 28, 30, 33, 34, 36]. Meanwhile, six studies included a total number patients larger than 200 [11, 28, 30–32, 34] and eight studies had the NOS score larger than 5 [26, 29–35]. The detailed characteristics of the included studies are summarized in Table 1. Moreover, the definition and cutoff values of sarcopenia from the included studies are summarized in Table 2.

Overall analyses of postoperative outcomes

Our pooled analyses indicated that patients with sarcopenia showed a significant longer hospital stay when compared to patients without sarcopenia after colorectal resection (WMD = 1.29, 95% CI = 0.50–2.08, $P < 0.01$). In terms of postoperative complications, the sarcopenia group showed a significantly higher total morbidity and mortality in comparison with the non-sarcopenia group (morbidity: OR = 1.70, 95% CI = 1.07–2.70, $P < 0.01$; mortality: OR = 3.45, 95% CI = 1.69–7.02, $P < 0.01$). Infection, anastomosis leakage and intestinal obstruction were the most common complications for patients after colorectal surgery and we observed that patients with sarcopenia showed a significant higher rate of incidence of postoperative infection but not anastomosis leakage and intestinal obstruction when compared with non-sarcopenia patients (infection: OR = 2.21, 95% CI = 1.50–3.25, $P < 0.01$; anastomosis leakage: OR = 0.73, 95% CI = 0.51–1.05, $P = 0.09$; OR = 1.13, 95% CI = 0.58–2.19, $P = 0.73$). The detailed results in terms of postoperative outcomes are shown in Fig. 2.

Overall analyses of survival outcomes

Six studies had provided survival outcome data [27, 28, 30–32, 35] and our pooled analyses demonstrated that the sarcopenia group showed a significant decreased OS in comparison with the non-sarcopenia group (HR = 1.63, 95% CI = 1.24–2.14, $P < 0.01$). In addition, we also observed that patients with sarcopenia had a significant decreased DFS and CSS in comparison with patients with non-sarcopenia after colorectal resection (DFS: HR = 1.70, 95% CI = 1.24–2.31, $P < 0.01$; CSS: HR = 1.62, 95% CI = 1.16–2.27, $P < 0.01$). The detailed results of survival outcomes are shown in Fig. 3. Moreover, five included studies had provided the results of multivariate analyses in OS [27, 28, 30, 31, 35], three studies in DFS [30, 31, 35], and three studies in CSS [28, 31, 35]; therefore, we pooled the results of multivariate analyses to further verify our overall results. The pooled results based on multivariate analyses data showed a similar tendency with our overall results significantly (OS: HR = 1.73, 95% CI = 1.28–2.35, $P < 0.01$; DFS: HR = 1.95, 95% CI = 1.36–2.80, $P < 0.01$; CSS: HR = 1.62, 95% CI = 1.16–2.27, $P < 0.01$).

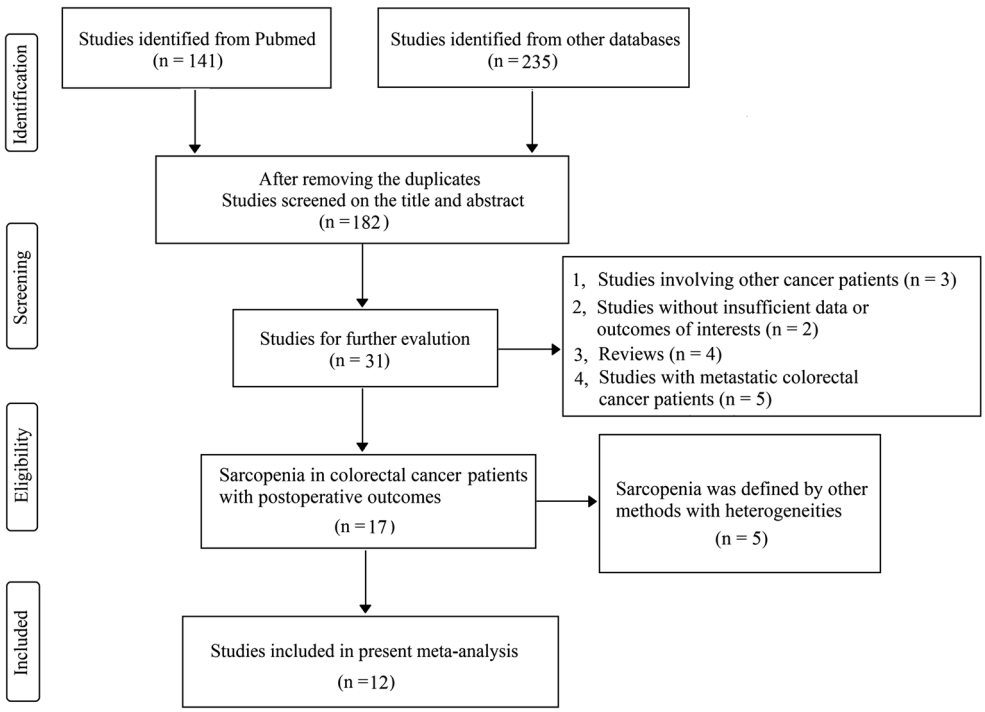

Fig. 1 Flow chart of included studies

Table 1 Characteristics of included studies

Author	Year	Study type	Country	Groups	Number	Age (years)	Male/female (%)	BMI (kg/m^2)	Stage	NOS
Lieffers et al. [11]	2012	Retrospective	Canada	Sarcopenia	91	Mean 66	63/37	Mean 26	II-IV	5
				Non-sarcopenia	143	Mean 61	55/45	Mean 30		
Choi et al. [27]	2018	Retrospective	South Korea	Sarcopenia	74	Mean 64	82/18	Mean 22	II-III	5
				Non-sarcopenia	114	Mean 60	49/51	Mean 25		
Chen et al. [26]	2018	Prospective	China	Sarcopenia	51	Mean 71	67/33	Mean 21	I-IV	6
				Non-sarcopenia	134	Mean 59	67/33	Mean 22		
Malietzis et al.[a] [30]	2016	Prospective	UK	Sarcopenia	485	Median 69	59/41	Median 27	I-IV	6
				Non-sarcopenia	320					
Huang et al. [29]	2015	Prospective	China	Sarcopenia	17	Mean 75	65/35	Mean 21	I-III	7
				Non-sarcopenia	125	Mean 60	62/38	Mean 23		
Nakanishi et al. [32]	2018	Retrospective	Japan	Sarcopenia	298	Mean 67	71/29	Mean 21	I-IV	6
				Non-sarcopenia	196	Mean 65	56/34	Mean 24		
Miyamoto et al.[a] [31]	2015	Retrospective	Japan	Sarcopenia	55	Median 70	61/39	Median 23	I-III	6
				Non-sarcopenia	165					
Pedziwiatr et al. [33]	2016	Prospective	Poland	Sarcopenia	34	Mean 70	65/35	Mean 23	I-IV	6
				Non-sarcopenia	90	Mean 65	32/68	Mean 27		
Reisinger et al.[a] [34]	2015	Retrospective	The Netherlands	Sarcopenia	148	51.3% > 70	58/42	58.7% > 25	I-IV	6
				Non-sarcopenia	162		NA			
van der Kroft et al.[a] [36]	2018	Prospective	The Netherlands	Sarcopenia	33	Mean 69	60/40	Mean 26	I-IV	5
				Non-sarcopenia	30		63/37			
Sueda et al. [35]	2018	Retrospective	Japan	Sarcopenia	51	NA	75/25	NA	I-III	6
				Non-sarcopenia	51		77/23			
Feliciano et al. [28]	2017	Retrospective	USA	Sarcopenia	1133	NA	NA	NA	I-III	5
				Non-sarcopenia	1337					

BMI body mass index, *NOS* Newcastle–Ottawa Scale, *NA* not applicable

[a] Studies only provided data of baseline information based on a whole population

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

Author	Definition and cutoff values of sarcopenia
Lieffers et al. [11]	Male: < 52.4 cm^2/m^2; female: < 38.5 cm^2/m^2
Choi et al. [27]	Male: < 52.4 cm^2/m^2; female: < 38.5 cm^2/m^2
Chen et al. [26]	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
Malietzis et al. [30]	Male: < 52.4 cm^2/m^2; female: < 38.5 cm^2/m^2
Huang et al. [29]	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
Nakanishi et al. [32]	Male: < 52.4 cm^2/m^2; female: < 38.5 cm^2/m^2
Miyamoto et al. [31]	Male: 32.6–49.5 cm^2/m^2; female: 15.6–42.1 cm^2/m^2
Pedziwiatr et al. [33]	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
Reisinger et al. [34]	Male: < 52.4 cm^2/m^2; female: < 38.5 cm^2/m^2
van der Kroft et al. [36]	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
Sueda et al. [35]	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
Feliciano et al. [28]	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)

BMI body mass index

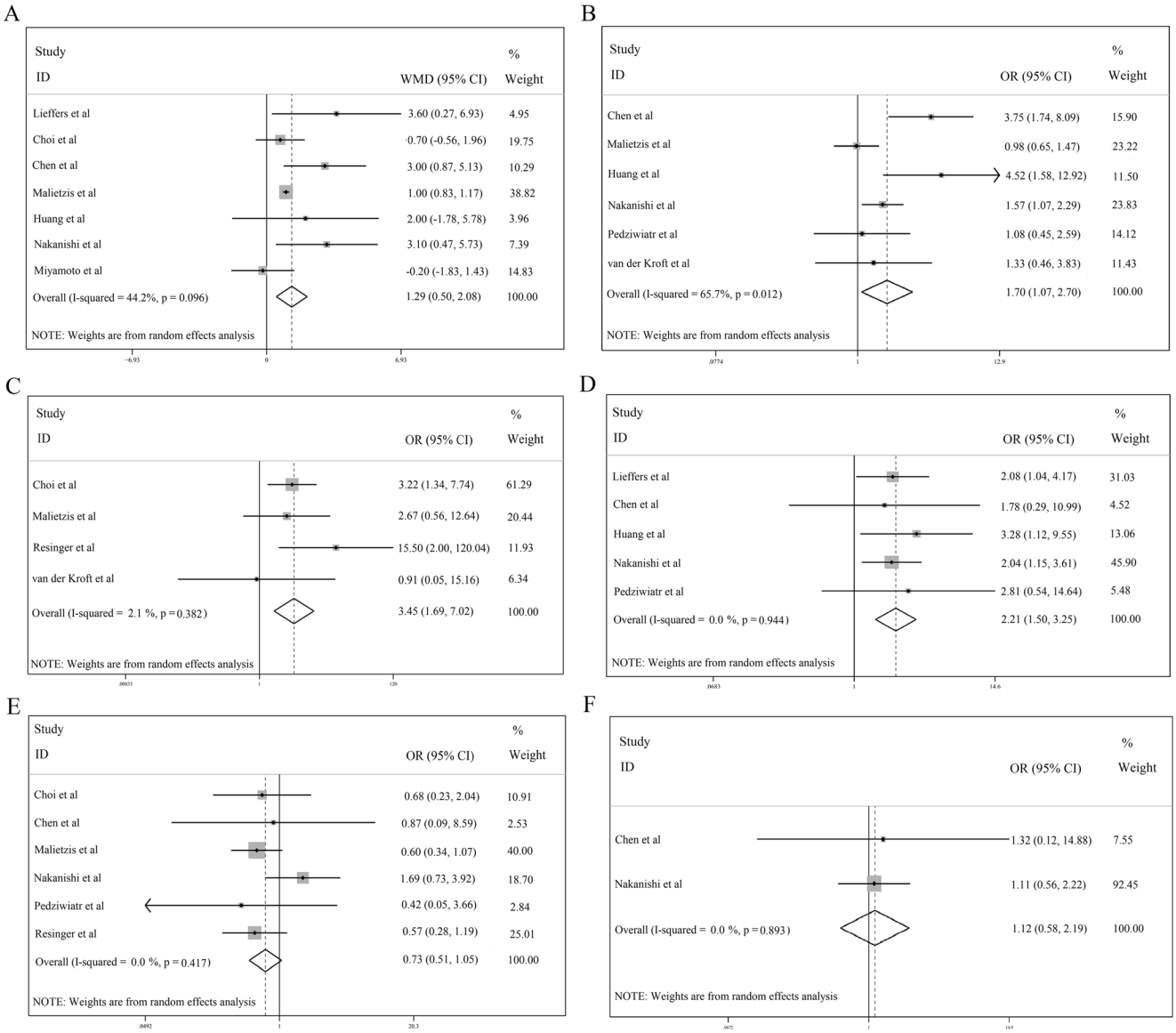

Fig. 2 Sarcopenia group versus non-sarcopenia group after colorectal resection based on postoperative outcomes. **a** Hospital stay, **b** total postoperative morbidity, **c** total postoperative mortality, **d** infection, **e** anastomosis leakage, **f** intestinal obstruction

Subgroup analyses and publication bias

Based on study type, total number of patients, NOS scores, country, and criterion of sarcopenia, we conducted subgroup analyses in terms of total postoperative complications and OS. Although we observed a similar tendency that the sarcopenia group had a higher incidence of postoperative complications and a decreased OS among different subgroups, some subgroups were without statistical significance. Regarding the total postoperative complications, the sarcopenia group showed a significantly higher incidence of postoperative complications in subgroups of retrospective studies (OR = 1.57, 95% CI = 1.08–2.29, $P = 0.02$), total patients smaller than 200 (OR = 2.24, 95% CI = 1.10–4.55, $P = 0.03$), NOS scores larger than 5 (OR = 1.77, 95% CI = 1.05–2.99, $P = 0.03$), studies conducted in Asia (OR = 2.69, 95% CI = 1.29–5.59, $P < 0.01$), and sarcopenia defined by SMI plus muscle strength and function (OR = 4.01, 95% CI = 2.16–7.44, $P < 0.01$). In addition, in terms of OS, except the subgroup of NOS scores larger than 5, all the other subgroups showed a significant improved OS in patients in the non-sarcopenia group. The detailed results of subgroup analyses are shown in Table 3. Meanwhile, we did not observe publication bias in terms of total postoperative complications (Begg's test: $P = 1.00$, Egger's test: $P = 0.32$) and OS (Begg's test: $P = 0.26$, Egger's test: $P = 0.10$) using Begg's and Egger's tests.

Discussion

Sarcopenia is a geriatric syndrome affecting older adults, which was first described by Rosenbery [37] as the loss of

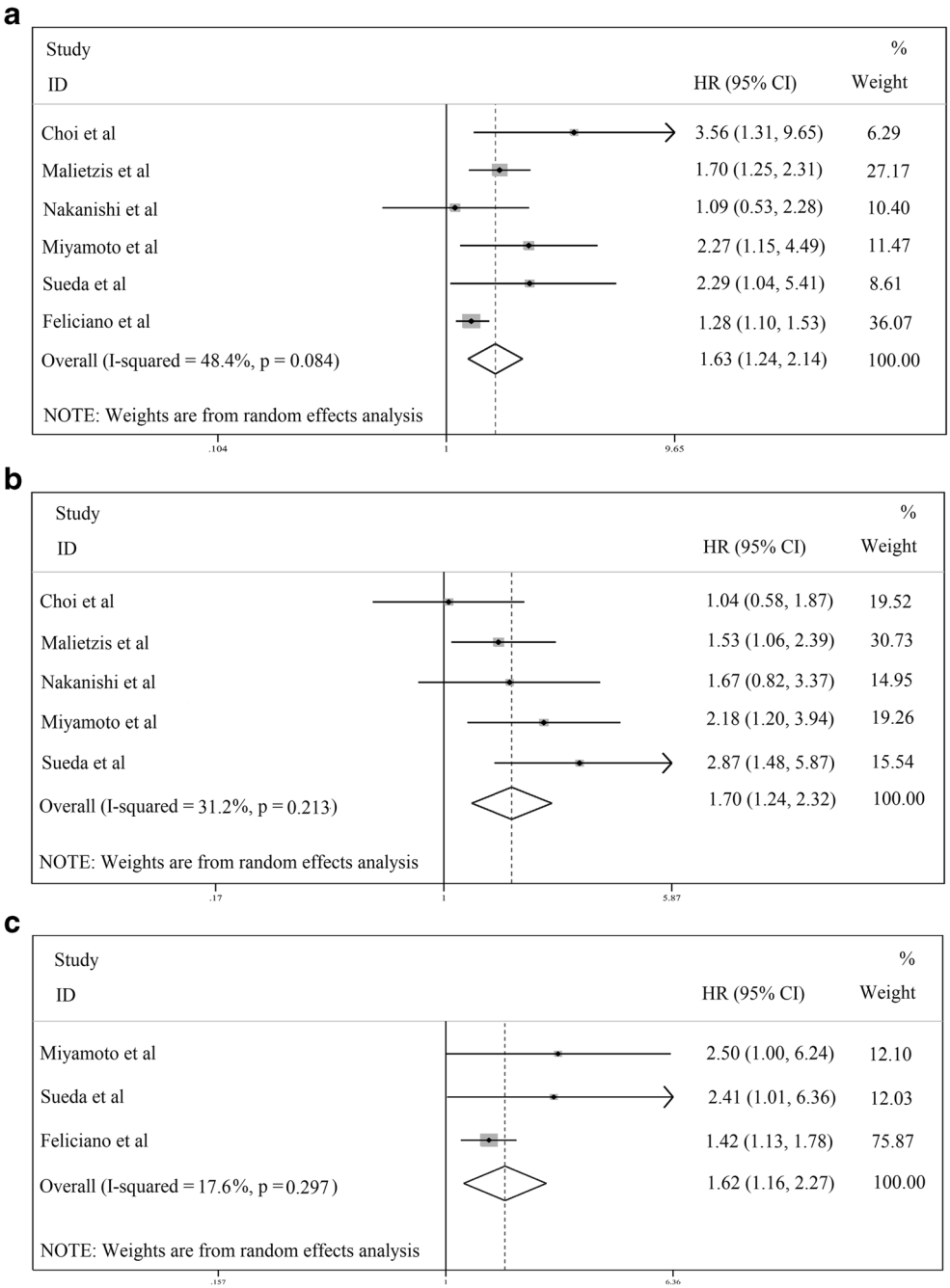

Fig. 3 Sarcopenia group versus non-sarcopenia group after colorectal resection based on survival outcomes. **a** Overall survival, **b** disease-free survival, **c** cancer-specific survival

muscle mass in seniors. Previous evidence indicated that sarcopenia can be a predictor of all-cause mortality among community-dwelling older people [38], and to date, the association between sarcopenia and cancer had drawn the attention of clinicians throughout the world. Recently, a systematic review indicated that low SMI at cancer diagnosis is associated with worse survival in patients with solid tumors [39]. However, to the best of our knowledge, whether sarcopenia can be a predictor of prognosis of CRC patients remains controversial; therefore, we conducted this systematic review and meta-analysis to resolve this issue.

Based on our results, we indicated that CRC patients with sarcopenia diagnosed with L3SMI would have longer hospital stays, higher incidence of total postoperative morbidity, mortality, and infections when compared to non-sarcopenia patients. Our results of the meta-analysis are in accordance with previous single-center investigation findings. Lieffers et al. indicated that sarcopenia is independently predictive of postoperative infections [11], and multivariate logistic regression analysis also showed that sarcopenia is significantly associated with total postoperative morbidity by studies of Huang et al. [29] and Nakanishi et al. [32]. Hence, sarcopenia not only

Table 3 Subgroup analyses in terms of overall survival and total postoperative complications

Characteristics	Total postoperative complications				Overall survival			
	n	OR (95% CI)	*P* value	Heterogeneity	*n*	HR (95% CI)	*P* value	Heterogeneity
Study type								
Retrospective	1	1.57 (1.08, 2.29)	0.02	NA	5	1.68 (1.15, 2.58)	< 0.01	50.8%
Prospective	5	1.80 (0.93, 3.49)	0.08	72.3%	1	1.70 (1.25, 2.31)	< 0.01	NA
Patients number								
≥ 200	2	1.25 (0.79, 1.98)	0.35	63.7%	4	1.46 (1.15, 1.86)	< 0.01	40.2%
< 200	4	2.24 (1.10, 4.55)	0.03	57.5%	2	2.74 (1.45, 5.17)	< 0.01	0.0%
NOS scores								
> 5	5	1.77 (1.05, 2.99)	0.03	72.5%	4	1.72 (1.34, 2.12)	0.20	74.5%
≤ 5	1	1.33 (0.46, 3.83)	0.59	NA	2	1.89 (0.71, 4.99)	< 0.01	0.0%
Country								
Asian	3	2.69 (1.29, 5.59)	< 0.01	69.2%	4	2.00 (1.26, 3.20)	< 0.01	28.0%
Non-Asian	3	1.03 (0.73, 1.46)	0.87	0.0%	2	1.43 (1.09, 1.88)	0.01	60.7%
Criterion of sarcopenia								
Only SMI	2	1.25 (0.79, 1.98)	0.35	63.7%	4	1.80 (1.27, 2.56)	< 0.01	27.7%
SMI based on BMI	2	1.18 (0.60, 2.31)	0.63	0.0%	2	1.48 (0.90, 2.42)	0.12	45.6%
SMI + strength + function	2	4.01 (2.16, 7.44)	< 0.01	0.0%	0	NA	NA	NA

OR odd radio, *HR* hazard radio, *SMI* skeletal mass index

negatively impacted the recovery of patients undergoing colorectal resection but also brought significant higher costs for relations of patients [40]. Moreover, sarcopenia is also a negative long-term prognostic factor for CRC patients based on our results. Evidence also demonstrated that sarcopenia in cancer survivors is associated with increased cardiovascular disease risk [41]. In addition, Nipp et al. also indicated that sarcopenia is associated with quality of life and depression in patients with advanced cancer [42]. Hence, the negative impacts of sarcopenia have highlighted the importance of prevention and curing sarcopenia among clinicians and patients.

What are the factors associated with the prevalence of sarcopenia in CRC patients? A recent investigation indicated that BMI, serum albumin, phase angle, muscle attenuation, and scored patients-generated subjective global assessment were independent predictors of sarcopenia in CRC patients by multivariable analyses [43]. Based on the baseline information of our included studies (Table 1), we also observed that patients in the sarcopenia group had a relatively lower BMI in comparison with non-sarcopenia group patients. Hence, changes in BMI may be a clinical signal for earlier detection of sarcopenia for CRC patients. Exercise and diet are the two main common ways for prevention of sarcopenia for cancer patients. Physical activity of cancer patients is associated with maintenance or significant improvements in aerobic capacity and muscle strength [44, 45]. Evidence also demonstrated that resistance exercise is more effective for improving muscle strength than aerobic exercise [44, 45]. In addition, there is indication that resistance training induces increase in muscle mass and strength can be enhanced by a high-protein diet and certain nutrients [46, 47].

A clear and uniformed definition of sarcopenia is important, since the number of publications on this syndrome is increasing. However, to date, no study has comprehensively evaluated the definitions and tools used in the literature to define and determine the presence of sarcopenia [14]. A systematic review on how to define and measure sarcopenia is being conducted and we expect the publication of this systematic review to standardize the criteria of sarcopenia [14]. To decrease the heterogeneity among studies caused by the diagnosis method of sarcopenia, we only included studies of sarcopenia diagnosed by preoperative CT scan with L3 SMI. Among the included studies, five studies defined the cutoff values only based on sex-specific L3 SMI, two studies also contained muscle strength and function assessments in addition to sex-specific L3 SMI, and five studies were based on both sex- and BMI-specific L3 SMI. Based on our subgroup analyses, we could still not determine the best criterion and cutoff values of sarcopenia for CRC patients because of the limited included studies and the lack of individual data. However, based on the current evidence, we proposed that gender, BMI and race should be taken into consideration for the cutoff values of the criteria of sarcopenia. In addition, muscle mass, strength, and function should be comprehensively evaluated to define sarcopenia.

In summary, our systematic review and meta-analysis has provided valid evidence in evaluating the significance of sarcopenia in patients after colorectal resection. However,

there are some limitations to our study. First, the definitions among studies were different and retrospective studies had no restriction with muscle strength and function. Although we conducted subgroup analyses based on definitions of sarcopenia and study type, prospective studies with uniform standards and definition of sarcopenia are needed to update our results. Second, neoadjuvant chemoradiotherapy and adjuvant chemotherapy were also important factors that affect the prognosis of CRC patients; however, included studies did not provide the detailed information and data based on neoadjuvant or adjuvant therapies. Hence, these factors might affect our pooled results and future studies based on individual data are needed to verify our findings. Finally, we could not conduct subgroup analyses based on the primary location of tumors, such as rectal, right, or left colon cancer. The prognosis was different based on the primary location of CRC patients [48]; therefore, the mixed baseline information might restrict our further exploration of the significance of sarcopenia in rectal and colon cancer, respectively.

Conclusion

Sarcopenia diagnosed by L3SMI can be a predictor of postoperative and survival outcomes for patients with CRC. However, prospective studies with uniform standards and definition of sarcopenia are needed to update our results.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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

Informed consent No informed consent.

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