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CT-assessed sarcopenia is a predictive factor for both long-term and short-term outcomes in gastrointestinal oncology patients: a systematic review and meta-analysis

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Abstract

Background: The impact of sarcopenia on the outcome of gastrointestinal (GI) oncological patients is still controversial. We aim to discuss the prevalence of sarcopenia and its relation to the oncological outcome.

Methods: Embase, Medline, PubMed, and the Cochrane library were systematically searched for related keywords. Studies using CT to assess sarcopenia and evaluate its relationship with the outcome of GI oncological patients were included. Long-term outcomes, including overall survival and disease-free survival, were compared by hazard ratios (HRs) with 95% confidence intervals (CIs). Short-term outcomes, including total complications and major complications (Clavien-Dindo ≥IIIa) after curable surgery, were compared by the risk ratio (RR) and 95% CI.

Results: A total of 70 studies including 21,875 patients were included in our study. The median incidence of sarcopenia was 34.7% (range from 2.1 to 83.3%). A total of 88.4% of studies used skeletal muscle index (SMI) in the third lumbar level on CT to define sarcopenia, and a total of 19 cut-offs were used to define sarcopenia. An increasing trend was found in the prevalence of sarcopenia when the cut-off of SMI increased (β = 0.22, 95% CI = 0.12–0.33, $p < 0.001$). The preoperative incidence of sarcopenia was associated both with an increased risk of overall mortality (HR = 1.602, 95% CI = 1.369–1.873, $P < 0.001$) and with disease-free mortality (HR = 1.461, 95% CI = 1.297–1.646, $P < 0.001$). Moreover, preoperative sarcopenia was a risk factor for both total complications (RR = 1.188, 95% CI = 1.083–1.303, P < 0.001) and major complications (RR = 1.228, 95% CI = 1.042–1.448, $P = 0.014$).

Conclusion: The prevalence of sarcopenia depends mostly on the diagnostic cut-off points of different criteria. Preoperative sarcopenia is a risk factor for both long-term and short-term outcomes.

Keywords: Sarcopenia, Gastrointestinal oncology, Nutrient, Operation

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Introduction

The incidence of gastrointestinal (GI) malignancy is almost 30% worldwide, with high cancer-related mortality [1, 2]. Aging is one of the most significant risk factors for the incidence and mortality in malignancy, usually with an exponential increase [2, 3]. Although there is great development in oncological treatment, surgical resection is still the main curable method [4]. However, for elderly oncologic patients, the incidence of postoperative complications still needs attention due to the nutrition status and potential comorbidities [5].

Sarcopenia was first proposed by Rosenberg in 1989 and was defined as a disease of skeletal muscle mass decline with age and was previously referred to as age-related sarcopenia [6, 7]. The incidence of sarcopenia is 20% in healthy people under 70 years of age, and its incidence is more than 50% after age 80 [8]. An epidemiological survey found that the incidence of muscle reduction in healthy elderly Chinese was 4.1–11.5%. A Japanese epidemiological study found that 14.2% of men and 22.1% of women in the elderly age range had muscle reduction [9]. There are many causes of sarcopenia, such as skeletal muscle disuse, endocrine changes, chronic consumptive diseases, systemic inflammatory response, insulin resistance, and malnutrition [10, 11]. GI cancer is often accompanied by an eating disorder and vomiting, coupled with increased metabolic consumption in the oncological condition, and the probability of malnutrition is higher. Therefore, the incidence of muscle reduction in patients with CRC is significantly higher than that in healthy people, reflecting that the tumor is one of the causes of sarcopenia [12]. Additionally, sarcopenia is a predictor of adverse outcomes in malignant tumors. Several studies have shown that muscle reduction is closely related to the incidence of postoperative complications and the overall survival of esophagus, gastrointestinal tract, hepatobiliary and pancreatic malignancies [13–16]. However, the impact of sarcopenia on the outcome of GI cancer patients remains controversial due to the heterogeneity of different studies, and negative results have been found in different populations [17, 18]. Thus, we designed this systematic review and meta-analysis to examine the prevalence of computed tomography (CT)-assessed sarcopenia in GI oncological patients and therefore discuss the relationship between sarcopenia and long-term and short-term outcomes in GI oncological patients.

Methods

This study was designed based on the preferred reporting items for systematic review and meta-analysis (PRISMA) guidelines [19].

Search strategy

A systematic review and meta-analysis were designed to evaluate CT-assessed sarcopenia in predicting the outcomes of gastrointestinal oncology patients. The Embase, Ovid Medline, Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Trials and PubMed were systematically searched up to March 25, 2019. In addition, the gray literature was searched using the related websites and Google Scholar. The keywords were designed by experienced librarians. Briefly, the key words included “sarcopenia”, “muscle mass”, “body composition” and “gastrointestinal”, “gastric”, “colorectal”, and “neoplasm”, “lesion”, “tumor”, “cancer” in Mesh and keywords. The search strategy is attached in appendix 1. All the studies containing abstracts and titles were imported into Endnote X6 to find duplicate studies and then for literature screening.

Inclusion and exclusion criteria

All the studies using CT-assessed sarcopenia or body composition in predicting long-term or short-term outcomes in GI oncology treatment patients were included in our study. The inclusion criteria were as follows: 1) the body composition was assessed by CT; 2) the study had a clear definition for sarcopenia or body composition, with a specific cut-off; 3) the outcome data and clinical data of GI oncological patients could be extracted; 4) GI oncology included esophageal, gastric, intestinal, and colorectal tumors; 5) the study mentioned one or more oncological treatments, such as surgery, chemotherapy, and radiation; 6) the study design was limited to randomized control trials, prospective or retrospective cohort studies, and case-control studies. Meta-analyses, reviews, conference abstracts and comments were read to find more papers. Only the studies written in English were included in the systematic review.

The exclusion criteria were as follows: 1) animal experiments; 2) body composition or sarcopenia assessed by other methods rather than CT; 3) no specific definition or cut-off of sarcopenia or body composition; 4) no available data of outcomes or the prevalence of sarcopenia in GI oncology patients; 5) cancer located in other organs rather than GI systems, such as liver, pancreas, and bladder; and 6) case reports or non-English publications. Data from the same center were treated as one dataset for further meta-analysis.

Literature screening and data extraction

Two investigators (H.Y.S. and T.F.C.) independently screened the abstracts and titles according to the inclusion and exclusion criteria. The full text was further evaluated if the abstract was not definitive. The third investigator (J.X.R.) was consulted for discussion if any disagreement existed.

A standard Excel spreadsheet was designed for data extraction, and the following information was collected from the original studies: the study characteristics

(author, publish year, country, institution, recruitment period, study design, etc.), patient characteristics (location of cancer, treatment, total sample, median age, sex distribution, tumor stage, etc.), assessment approach of sarcopenia or body composition (modality, CT-specific index, definition and cut-off of index), sarcopenia prevalence and outcome assessment (complication rate after surgery, toxicity and progression rate after adjuvant therapy, overall survival and disease-free survival after treatment). The complication after surgery was evaluated based on the Clavien-Dindo criteria, and a major complication was defined as stage IIIa or higher [20].

Quality assessment

Two reviewers (E.Y.L. and L.J.S.) independently assessed the quality of the included papers. For case-control and cohort studies, the Newcastle-Ottawa Scale (NOS) was used to evaluate the quality. High quality was defined as a score greater than 7, and moderate quality was defined as a score between 5 and 7 [21]. Moreover, the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system was used to evaluate the overall quality of the evidence [22].

Assessment approach of body composition

The CT-quantified muscle mass area was used to assess the sarcopenia. Different criteria, including the skeletal muscle index (SMI), which calculated the area of total skeletal muscle (cm^2) in the third lumbar (L3) level divided by the height squared (m^2), total psoas area (TPA), and visceral fat volume and area (VFV, VFA), were commonly used to describe the nutritional status of patients.

Statistical analysis

The statistical analysis was performed by Stata 15.0 software (Stata Corporation, College station, TX, USA). The prevalence of sarcopenia in different studies was drawn in bubble plots, with the relative sample as the bubble size. Linear trends were analyzed using weighted least squares regression using prevalence as the dependent variable and cut-off of SMI in females as the independent variable with sample size as the weight. The complications were compared and combined using relative risk (RR), while the survival analysis was combined using hazard ratio (HR). Both were reported with a 95% confidence interval (CI), and a P value less than 0.05 was set as significant. The I^2 statistic and χ^2 test were used for heterogeneity assessment ($I^2 \geq 50\%$ indicating the presence of heterogeneity). When heterogeneity existed, the random-effect model was used, while the fixed-effect model was used otherwise. Finally, forest plots were drawn, and funnel plots were used to evaluate the publication bias.

Results

Literature selection

A total of 2942 studies were found according to the search strategy. The flowchart is shown in Fig. 1. After screening the abstracts and titles, 156 studies were scanned in full. After excluding the incompatible studies, a total of 70 studies were included in the systematic review [6, 13–15, 17, 18, 23–86].

Characteristics of the included studies

The characteristics of the included studies are shown in Table 1. The first study using body composition to predict the outcomes after treatment in GI oncological patients

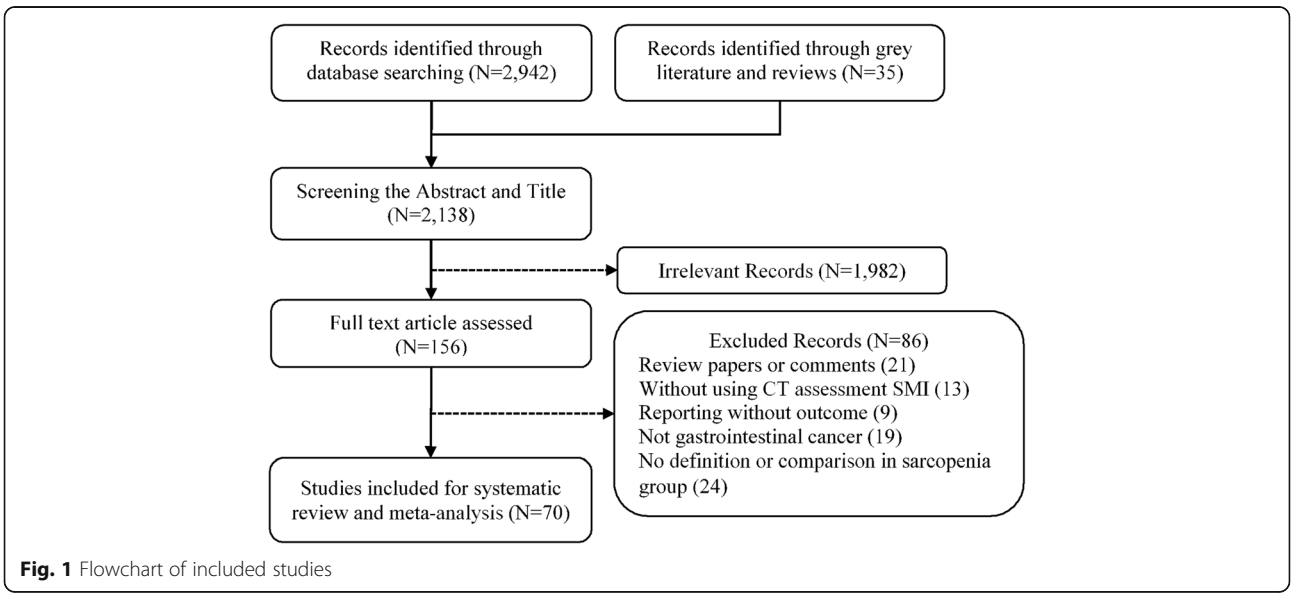

Fig. 1 Flowchart of included studies

Table 1 Characteristics of included studies

Author	Year	Recruitment period	Design	Disease	Treatment	Total sample	Median age, year	Tumor stage (AJCC, I/II/III/IV)	Male, n (%)	Adjuvant therapy, n (%)
Yang, J.	2019	2011–2017	Retrospective	CRC	Surgery	417	57.9	80/190/149/0	251 (60)	–
Hopkins, J. J.	2019	2007–2009	Retrospective	CRC	Surgery	968	65.8	100/374/494/0	589 (61)	503 (52)
van Vugt, J. L. A.	2018	2007–2013	Retrospective	CRC	Surgery	816	–	255/293/269	440 (54)	158 (19)
van der Kroft, G.	2018	2012–2013	Retrospective	CRC	Surgery	63	–	18/13/20/12	39 (62)	–
Mosk, C. A.	2018	2013–2015	Retrospective	CRC	Surgery	251	76	–	141 (56)	26 (10)
Mauricio, S. F.	2018	2013–2016	Retrospective	CRC	Surgery	84	61.6	36/48 [a]	39 (46)	51 (61)
Martin, L.	2018	2013–2015	Retrospective	CRC	Surgery	210	66.6	385/713/887/109	1270 (60)	–
Chen, W. Z.	2018	2014–2017	Retrospective	CRC	Surgery	376	64.3	65/155/145/11	228 (61)	–
Feliciano, E. M. C.	2017	2006–2011	Prospective	CRC	Surgery	247	63	690/806/956/0	1251 (51)	–
Black, D.	2017	2006–2014	Retrospective	CRC	Surgery	339		58/153/128/0	181 (53)	66 (19)
Ouchi, A.	2016	2012–2015	Retrospective	CRC	Surgery	60	69	42/18 [a]	35 (58)	–
Malietzis, G.	2016	2006–2013	Retrospective	CRC	Surgery	805	69	189/265/267/84	472 (59)	182 (23)
Reisinger, K. W.	2015	2010–2012	Retrospective	CRC	Surgery	310	–	–	155 (50)	–
Park, B. K.	2015	2005–2012	Retrospective	CRC	Surgery	543	–	185/314 [a]	311 (57)	51 (9)
Miyamoto, Y.	2015	2005–2010	Retrospective	CRC	Surgery	220	–	77/84/59/0		54 (25)
Huang, D. D.	2015	2014–2015	Retrospective	CRC	Surgery	142	62	–	88 (62)	5 (4)
Lieffers, J. R.	2012	2002–2006	Retrospective	CRC	Surgery	234	63	0/74/83/77	135 (58)	–
Pedziwiatr, M.	2016	2014–2015	Retrospective	CRC	Surgery	124	65.9	32/32/39/21	73 (59)	–
Jones, K. I.	2015	2011–2012	Retrospective	CRC	Surgery	100	68.6	–	60 (60)	–
Guinan, E. M.	2018	2014–2016	Retrospective	EC	Surgery	27	–	–	–	27 (100)
Mayanagi, S.	2017	2004–2013	Prospective	EC	Surgery	66	63.3	0/27/39/0	57 (86)	66 (100)
Elliott, J. A.	2017	2010–2015	Retrospective	EC	Surgery	207	61.6	–	165 (80)	207 (100)
Black, D.	2017	2006–2014	Retrospective	EC	Surgery	108	–	30/43/35/0	74 (69)	65 (60)
Nishigori, T.	2016	2005–2014	Retrospective	EC	Surgery	199	–	33/99/63/6	164 (82)	–
Grotenhuis, B. A.	2016	2001–2012	Retrospective	EC	Surgery	120	62	–	88 (73)	120 (100)
Yip, C.	2014	NG	Retrospective	EC	Surgery	35	63	0/10/23/2	30 (86)	35 (100)
Nakashima, Y.	2018	2004–2014	Retrospective	EC	Surgery	341	–	38/46/55/33	289 (85)	–
Paireder, M.	2017	2006–2013	Retrospective	EC	Surgery	130	61.4	15/22/76/3	106 (82)	130 (100)
Tamandl, D.	2016	2006–2013	Retrospective	EC	Surgery	200	63.9	45/33/95/4	151 (76)	–
Harada, K.	2016	2005–2011	Retrospective	EC	Surgery	325	–	129/45/128/23	298 (92)	–
Tan, B. H.	2015	2010–2012	Retrospective	EC	Surgery	89	65.8	21/27/41/0	67 (75)	89 (100)
Zhang, Y.	2019	2015–2017	Retrospective	GC	Surgery	156	59.1	48/27/81/0	115	35 (22)

Table 1 Characteristics of included studies *(Continued)*

Author	Year	Recruitment period	Design	Disease	Treatment	Total sample	Median age, year	Tumor stage (AJCC, I/II/III/IV)	Male, n (%)	Adjuvant therapy, n (%)
									(74)	
Zhang, W. T.	2018	2014–2016	Prospective	GC	Surgery	636	–	203/140/293/0	478 (75)	–
Wang, S. L.	2018	2009–2013	Retrospective	GC	Surgery	859	64	239/193/427/0	672 (78)	–
Park, H. S.	2018	2006–2009	Retrospective	GC	Surgery	136	55	0/57/79/0	96 (71)	63 (46)
O'Brien, S.	2018	2008–2014	Retrospective	GC	Surgery	56	68.4	18/13/18/0	41 (73)	28 (50)
Nishigori, T.	2018	2005–2013	Retrospective	GC	Surgery	177	–	0/100/77/0	127 (72)	127 (72)
Mao, C. C.	2018	2014–2016	Prospective	GC	Surgery	682	64.6	–	513 (75)	–
Lin, J.	2018	2015–2016	Prospective	GC	Surgery	670	65	–	–	–
Choi, M. H.	2018	2007–2009	Retrospective	GC	Surgery	98	–	–	–	–
Beuran, M.	2018	2014–2016	Retrospective	GC	Surgery	78	–	6/28/41/13	–	–
Zhou, C. J.	2017	2014–2015	Retrospective	GC	Surgery	240	73	74/55/111/0	190 (79)	–
Zheng, Z. F.	2017	2009–2013	Retrospective	GC	Surgery	639		–	525 (82)	408 (64)
Lou, N.	2017	2014–2015	Retrospective	GC	Surgery	206	64.1	80/45/81/0	161 (78)	–
Kudou, K.	2017	2005–2016	Retrospective	GC	Surgery	148	–	–	–	–
Huang, D. D.	2017	2014–2015	Retrospective	GC	Surgery	470	65	163/103/204/0	364 (77)	–
Zhuang, C. L.	2016	2008–2013	Retrospective	GC	Surgery	937	64	271/219/447	730 (78)	–
Wang, S. L.	2016	2014–2015	Prospective	GC	Surgery	255	65.1	81/48/126/0	190 (75)	–
Takeuchi, M.	2016	2009–2015	Retrospective	GC	Surgery	75	–	25/16/28/6	57 (76)	3 (4)
Huang, D. D.	2016	2014–2015	Prospective	GC	Surgery	173	72	53/40/80/0	135 (78)	–
Tegels, J. J.	2015	2005–2012	Retrospective	GC	Surgery	152	69.6	42/27/47/57	87 (57)	71 (47)
Li, X. T.	2015	2005–2008	Retrospective	GC	Surgery	84	57	0/31/53/0	60 (71)	–
Sakurai, K.	2017	2007–2013	Retrospective	GC	Surgery	569	66.7	264/121/126/58	396 (70)	91 (16)
Chen, F. F.	2016	2014–2016	Prospective	GC	Surgery	158	66.9	33/37/88/0	126 (80)	–
Takeda, Y.	2018	2004–2011	Retrospective	RC	Surgery	144	–	0/45/99/0	102 (71)	63 (44)
Park, S. E.	2018	2005–2015	Retrospective	RC	Surgery	65	71	8/24/27/0	46 (71)	65 (100)
Choi, M. H.	2018	2009–2013	Retrospective	RC	Surgery	188	61.3	0/34/154/0	117 (62)	188 (100)
Heus, C.	2016	2006–2013	Retrospective	RC	Surgery	74	64	–	39 (53)	–
Souza, B. U.	2018	2015–2016	Retrospective	CRC	All	197	60.5	54/138 [a]	112 (57)	–
Kurk, S. A.	2018	NG	Prospective	CRC	AT	450	–	–	285 (63)	n/a
Chemama, S.	2016	2008–2010	Retrospective	CRC	AT	97	53	–	37 (38)	n/a
Blauwhoff-Buskermolen, S.	2016	2011–2014	Retrospective	CRC	AT	67	66.4	–	42 (63)	n/a
Barret, M.	2014	NG	Retrospective	CRC	AT	51	65	–	38 (75)	n/a

Table 1 Characteristics of included studies *(Continued)*

Author	Year	Recruitment period	Design	Disease	Treatment	Total sample	Median age, year	Tumor stage (AJCC, I/II/III/IV)	Male, n (%)	Adjuvant therapy, n (%)
Guiu, B.	2010	2002–2008	Retrospective	CRC	AT	120	–	–	55 (46)	n/a
Anandavadivelan, P.	2016	2006–2012	Retrospective	EC	AT	72	–	2/20/50/0	–	n/a
Awad, S.	2012	NG	Retrospective	EC	AT	47	–	–	34 (72)	n/a
Sugiyama, K.	2018	2013–2015	Retrospective	GC	AT	118	64	–	59 (50)	n/a
Palmela, C.	2017	2012–2014	Retrospective	GC	AT	47	68	0/5/42/0	32 (68)	n/a
Mirkin, K. A.	2017	2000–2015	Retrospective	GC	AT	41	–	–	–	n/a
Hayashi, N.	2016	2009–2014	Retrospective	GC	AT	53	–	–	–	n/a
Nipp, R. D.	2018	2011–2015	Retrospective	GIC	AT	103	–	–	–	n/a

Abbreviation: *EC* esophageal cancer, *GC* gastric cancer, *GIC* gastrointestinal cancer, *CRC* colorectal cancer, *RC* rectal cancer, *AT* adjuvant or neo-adjuvant therapy, *NG* not given, *n/a* not available
[a]Tumor stage I and II versus III and IV

was published in 2010 [77], while the first study using SMI to define sarcopenia was published in 2012 [75]. Sixty-two studies were retrospective, and eight were prospective, with a recruitment period between 2001 and 2017. A total of 21,875 patients were involved in the systematic review: 1996 esophageal cancer (EC) patients (14 studies), 7913 gastric cancer (GC) patients (27 studies) and 11,875 CRC patients (29 studies). Twelve studies enrolled advanced oncological patients who only received adjuvant treatment, while fifty-seven studies involved patients who underwent surgery combined with adjuvant treatment or not, and the percentage of adjuvant treatment prior or after surgery ranged from 4 to 100%. The median age was 64.6 years (range from 53 to 76 years), and the percentage of male patients ranged from 38 to 92%. The prevalence ranges of tumor stages I, II, and III were 2.78–46.39%, 10.63–56.49%, and 16.12–89.36%.

Sarcopenia definition, assessment of prevalence

The studies were mainly from Asia, Europe, North America, and South America, including 15 counties (Austria, Brazil, Canada, China, France, Ireland, Japan, Korea, Netherland, Poland, Portugal, Romania, Sweden, UK and USA). The common cut-offs for evaluating the sarcopenia are listed in Table 2. The median incidence of sarcopenia was 34.7% (range from 2.1 to 83.3%). The majority of studies (88.4%) used SMI in L3 to assess sarcopenia, five studies used visceral fat criteria, and three studies used TPA criteria. Among the studies using SMI, three main criteria were the most commonly adopted criteria, including 47 studies. The cut-off of SMI introduced by Prado et al. in 2008 (sarcopenia was defined as SMI < 52.4 cm^2/m^2 for males and SMI < 38.5 cm^2/m^2 for females) was used in 20 studies covering 10 countries [23, 30, 34, 35, 43–45, 47, 52, 57, 61, 62, 64, 67, 69, 73–76, 85]. The prevalence of sarcopenia ranged from 7.4 to 83.3% (7.4–71.8% in non-Asian countries, with a median prevalence of 40.1%; 14.6–83.3% in Asian countries, with a median prevalence of 52.7%). The cut-off provided by Martin et al. in 2013 (sarcopenia was defined as SMI < 41 cm^2/m^2 in females; SMI < 53 cm^2/m^2 if BMI ≥ 25 kg/m^2 and SMI < 43 cm^2/m^2 if BMI < 25 kg/m^2 in males) was used in 17 studies covering 9 Asian and non-Asian countries [6, 24, 28, 31, 33, 35, 37, 38, 42, 50, 54, 58, 65, 66, 68, 81, 82]. The prevalence of sarcopenia ranged from 14.7 to 69.8% (14.7–56.7% in non-Asian countries, with a median prevalence of 35.1%; 28.4–69.8% in Asian countries, with a median prevalence of 43.4%). The cut-off introduced by Zhuang et al. was generally used in Asian countries (12 studies: [13, 25, 26, 35, 40, 41, 46, 48, 53, 55, 63, 84]), which defined sarcopenia as SMI < 40.8 cm^2/m^2 in males and SMI < 34.9 cm^2/m^2 in females, but the majority of the studies were from the same center. The prevalence ranged from 6.8–41.5%, with a median of 23.1%. The cut-off provided by Iritani et al. was used in three studies (SMI < 36 cm^2/m^2 in male; SMI < 29 cm^2/m^2 in female) with a median prevalence of 9.3% [35, 59, 72], and the cut-off provided by Voron et al. was also used in three studies (SMI < 55 cm^2/m^2 in male; SMI < 39 cm^2/m^2 in female) with a median prevalence of 53.6% [36, 79, 80]. Two other Japanese studies adopted the cut-off from Sakurai et al. (SMI < 43.2 cm^2/m^2 in males; SMI < 34.6 cm^2/m^2 in females) and had a median prevalence of 23.5% [18, 35]. The prevalence of sarcopenia is plotted in Fig. 2, and an increasing trend was found in the prevalence of sarcopenia as the cut-off of SMI increased ($\beta = 0.22$, 95% CI = 0.12–0.33, $p < 0.001$, $r^2 = 0.2170$).

Quality assessment

The quality assessment is available in Table 2 and shows the study quality ranging from low to high quality, with scores ranging from 4 to 8 on the NOS scale. Eight studies were considered high quality, with a score of 8 [13, 18, 28, 54, 64, 72, 78, 79], fifty-three

Table 2 Sarcopenia definition, assessment and prevalence

No	Modality	Index	Cut-off, Male	Cut-off, Female	Method	Prevalence	Reference	Country	NOS
1	CT/L3	SMI	32.5	28.6	Cut-off from 3-year overall survival	16.1%	Zheng, Z. 2017	China	7
2	CT/L3	SMI	36	29	Cut-off from Iritani et al.	3.4%	Nishigori, T. 2018	Japan	7
						12.5%	Wang, S. 2016	China	7
						12.0%	Huang, D. 2015	China	8
3	CT/L3	SMI	40.8	34.9	Cut-off from Zhuang et al.	15.4%	Zhang, Y. 2019	China	7
						19.7%	Zhang, W. 2018	China	6
						17.5%	Nishigori, T. 2018	Japan	7
						19.4%	Mao, C. 2018	China	6
						15.5%	Lin, J. 2018	China	5
						24.5%	Chen, W. 2018	China	7
						28.8%	Zhou, C. 2017	China	7
						6.8%	Lou, N. 2017	China	7
						37.4%	Huang, D. 2017	China	7
						41.5%	Zhuang, C. 2016	China	8
						30.1%	Huang, D. 2016	China	7
						24.7%	Chen, F. 2016	China	6
4	CT/L3	SMI	43.2	34.6	Cut-off from Sakurai et al.	22.0%	Nishigori, T. 2018	Japan	7
						25.0%	Sakurai, K. 2017	Japan	8
5	CT/L3	SMI	44.5	36.5	Cut-off from the third quartile cases	25.8%	Harada, K. 2016	Japan	6
6	CT/L3	SMI	45	33.8	Cut-off from the third quartile cases	25.7%	Takeda, Y. 2018	Japan	7
7	CT/L3	SMI	47.2	36.9	Cut-off from the median of SMI	49.9%	Nakashima, Y. 2018	Japan	8
8	CT/L3	SMI	49	31	Cut-off from Kim et al.	38.5%	Park, S. 2018	Korea	6
9	CT/L3	SMI	49.5	42.1	Cut-off from the third quartile cases	25.0%	Miyamoto, Y. 2015	Japan	7
10	CT/L3	SMI	52.4	38.9	Cut-off from Prado et al.	14.6%	Yang, J. 2019	China	6
						35.7%	O'Brien, S. 2018	Ireland	7
						64.4%	Nishigori, T. 2018	Japan	7
						7.4%	Guinan, E. 2018	Ireland	4
						39.4%	Choi, M. 2018	Korea	7
						39.8%	Choi, M. 2018	Korea	6
						71.8%	Beuran, M. 2018	Romania	5
						83.3%	Mayanagi, S. 2017	Japan	7
						23.7%	Elliott, J. 2017	Ireland	6
						74.9%	Nishigori, T. 2016	Japan	7
						60.2%	Malietzis, G. 2016	UK	7
						45.0%	Grotenhuis, B. 2016	Netherlands	8
						43.1%	Anandavadivelan, P. 2016	Swede	5
						47.7%	Reisinger, K. 2015	Netherlands	6
						25.7%	Yip, C. 2014	UK	5
						38.9%	Lieffers, J. 2012	Canada	7
						2.1%	Awad, S. 2012	UK	4

Table 2 Sarcopenia definition, assessment and prevalence *(Continued)*

No	Modality	Index	Cut-off, Male	Cut-off, Female	Method	Prevalence	Reference	Country	NOS
						49.4%	Tan, B. 2015	UK	5
							Sugiyama, K. 2018	Japan	5
11	CT/L3	SMI	55.4	38.9	Cut-off from Prado et al.	70.6%	Barret, M. 2014	France	5
12	CT/L3	SMI	55	39	Cut-off from Voron et al.	57.3%	Nipp, R. 2018	USA	4
						38.5%	Paireder, M. 2017	Austria	8
						65.0%	Tamandl, D. 2016	Austria	7
13	CT/L3	SMI	43/53 (BMI lower or higher than 25)	41	Cut-off from Martin et al.	27.5%	Hopkins, J. 2019	Canada	7
						50.5%	van Vugt, J. 2018	Netherlands	8
						52.4%	van der Kroft, G. 2018	Netherlands	6
						14.7%	Souza, B. 2018	Brazil	4
						32.4%	Park, H. 2018	Korea	6
						42.9%	Nishigori, T. 2018	Japan	7
						24.3%	Mosk, C. 2018	Netherlands	6
						34.5%	Mauricio, S. 2018	Brazil	7
						38.0%	Kurk, S. 2018	Netherlands	4
						23.4%	Palmela, C. 2017	Portugal	4
						28.4%	Kudou, K. 2017	Japan	8
						21.3%	Black, D. 2017	UK	7
						23.9%	Black, D. 2017	UK	7
						40.2%	Chemama, S. 2016	France	6
						56.7%	Blauwhoff-Buskermolen, S. 2016	Netherlands	6
						56.6%	Tegels, J. 2015	Netherlands	6
						27.4%	Pedziwiatr, M. 2016	Poland	7
						69.8%	Hayashi, N. 2016	Japan	6
14	CT/L3	SMI	52/54 (BMI lower or higher than 30)	38/47 (BMI lower or higher than 30)	Cut-off from Caan et al.	45.9%	Feliciano, E. 2017	USA	6
15	CT/L3	SMI	–	–	z-score below - 0.5 for SMI in different ages	6.7%	Martin, L. 2018	Canada	6
16	CT/L3	TPA	538	346	normal TPA in the lowest sex-specific quartile	33.3%	Ouchi, A. 2016	Japan	6
17	CT/L3	TPA	545	385	Cut-off from Fearon et al.	29.3%	Mirkin, K. 2017	USA	5
						15.0%	Jones, K. 2015	UK	4
18	CT	VEV	1.92	1.92	Cut-off from the quartiles	25.0%	Park, B. 2015	Korea	5
19	CT	VFA	100	100	Cut-off from the Japanese Society for study of Obesity	35.9%	Wang, S. 2018	China	7
						65.3%	Takeuchi, M. 2016	Japan	6
						40.5%	Heus, C. 2016	Netherlands	4

Abbreviation: *CT/L3* the third lumbar vertebra level in CT scan, *BMI* body mass index, *SMI* skeletal muscle index, *TPA* total psoas muscle area, *VEV* visceral fat volume, *VFA* visceral fat area

studies were considered moderate quality, with a score ranging from 5 to 7 [6, 15, 17, 23–27, 29, 30, 32–35, 37–41, 44–49, 51–53, 55–63, 65–71, 73–75, 80–85], and the remaining 9 studies were given a score of 4 and considered low quality [14, 31, 36, 42, 43, 50, 76, 77, 86]. According to the GRADE, the overall quality of the evidence of sarcopenia as a predictive factor for both long-term and short-term should be considered "very low" due to the lack of randomized control trials.

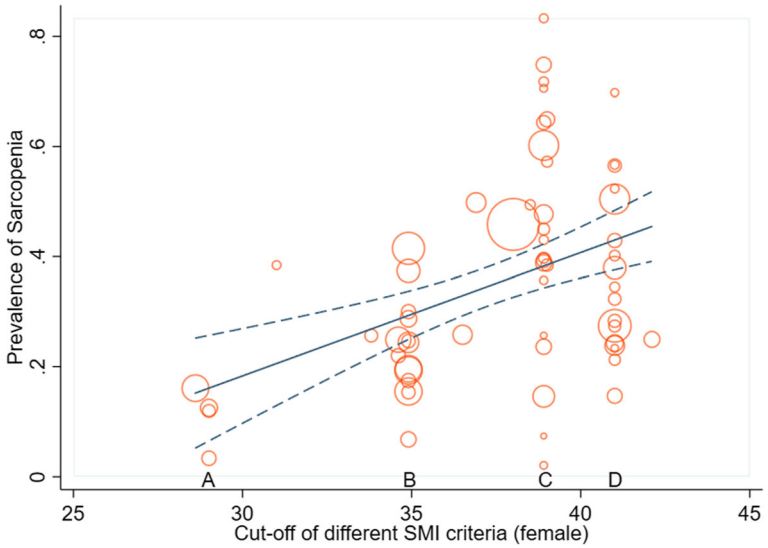

Fig. 2 The bubble plots and linear relationship between the prevalence of sarcopenia and the cut-offs for females under different criteria (A. cut-off from Iritani et al.; B. cut-off from Zhuang et al.; C. cut-off from Prado et al.; D. cut-off from Martin et al.)

Long-term outcome assessment

The forest plot of long-term outcomes after surgery in GI oncology patients is shown in Fig. 3. A total of 20 studies were included for assessing the risk for overall survival (OS) (Fig. 3a), and 11 studies were included for disease-free survival (DFS) (Fig. 3b). The preoperative incidence of sarcopenia was associated both with an increased risk of overall mortality (HR = 1.602, 95% CI = 1.369–1.873, $P < 0.001$, $I^2 = 59.5\%$, random-effect model) and disease-free mortality (HR = 1.461, 95% CI = 1.297–1.646, $P < 0.001$, $I^2 = 0\%$, fixed-effect model).

The subgroup analysis is shown in Table 3. Due to the different body shapes, we compared the Asian countries and non-Asian countries. Moreover, three main criteria and three main diseases, CRC, EC and GC, were compared. In terms of OS, the preoperative incidence of sarcopenia was associated with higher overall mortality in both Asian and non-Asian populations (HR = 1.776 and 1.368, $P < 0.001$ and $P = 0.002$, respectively). Preoperative sarcopenia using cut-offs provided by Zhang et al. and Martin et al. increased the risk of overall mortality (HR = 1.622 and 1.343, respectively, both $P < 0.001$), while no statistically significant increase was observed using the cut-off provided by Prado et al. (HR = 1.976, $P = 0.075$). In terms of the tumor in the three different locations, preoperative sarcopenia was always a risk factor increasing the overall mortality (HR = 1.523, 1.567, and 1.703, $P = 0.001$, 0.015 and < 0.001 in CRC, EC and GC surgical patients, respectively). In terms of DFS, the preoperative incidence of sarcopenia was also associated with a higher risk of disease-free mortality in both Asian and non-

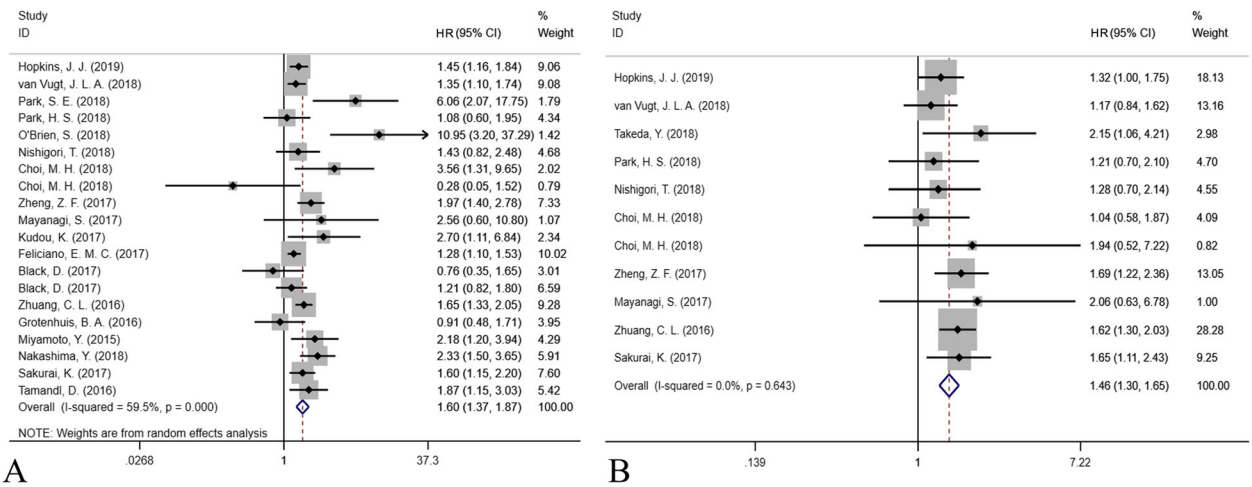

Fig. 3 The forest plot for assessing the impact of sarcopenia on long-term outcomes (**a**. overall survival; **b**. disease-free survival)

Table 3 The results of subgroup meta-analysis

Subgroup	Cohort	HR or RR	95%CI	P value	I2
Long-term outcome (HR)-Overall survival					
Overall	20	1.602	1.369–1.873	< 0.001	59.5%
Asian countries	12	1.776	1.556–2.026	< 0.001	41.9%
Non-Asian countries	8	1.368	1.117–1.676	0.002	60.1%
Zhuang criteria	2	1.622	1.326–1.983	< 0.001	0%
Martin criteria	5	1.343	1.200–1.503	< 0.001	0%
Prado criteria	6	1.976	0.934–4.182	0.075	74.2%
CRC surgery	7	1.523	1.201–1.930	0.001	63.1%
EC surgery	5	1.567	1.089–2.253	0.015	52.9%
GC surgery	8	1.703	1.281–2.262	< 0.001	60.6%
Long-term outcome (HR)-Disease-free survival					
Overall	11	1.461	1.297–1.646	< 0.001	0%
Asian countries	9	1.566	1.357–1.808	< 0.001	0%
Non-Asian countries	2	1.255	1.014–1.553	0.037	0%
Zhuang criteria	2	1.568	1.274–1.930	< 0.001	0%
Martin criteria	3	1.249	1.024–1.523	0.028	0%
Prado criteria	3	1.271	0.778–2.075	0.338	0%
CRC surgery	4	1.282	1.058–1.554	0.011	0%
EC surgery	1	2.060	0.626–6.783	0.235	–
GC surgery	6	1.578	1.355–1.839	< 0.001	0%
Short-term outcome (RR)-Total complication after surgery					
Overall	15	1.188	1.083–1.303	< 0.001	26.4%
Asian countries	10	1.165	1.046–1.298	0.005	43.9%
Non-Asian countries	5	1.252	1.045–1.499	0.015	0%
Zhuang criteria	4	1.423	1.214–1.667	< 0.001	0%
Martin criteria	5	1.246	1.017–1.527	0.034	0%
Prado criteria	2	1.074	0.842–1.371	0.565	0%
CRC surgery	6	1.314	1.101–1.568	0.002	0%
EC surgery	4	1.051	0.900–1.226	0.531	0%
GC surgery	5	1.218	1.046–1.419	0.011	61.9%
Short-term outcome (RR)-Major complication after surgery					
Overall	14	1.228	1.042–1.448	0.014	12.1%
Asian countries	7	1.244	1.001–1.545	0.049	45.9%
Non-Asian countries	7	1.206	0.936–1.553	0.148	0%
Zhuang criteria	2	2.084	1.359–3.196	0.001	50%
Martin criteria	5	0.988	0.690–1.413	0.946	0%
Prado criteria	4	1.309	0.978–1.750	0.070	0%
CRC surgery	4	0.899	0.545–1.481	0.675	0%
EC surgery	4	1.181	0.932–1.495	0.169	0%
GC surgery	6	1.393	1.076–1.803	0.012	48.3%

Abbreviation: *RR* relative risk, *HR* hazard ratio, *CI* confidence interval, *EC* esophageal cancer, *GC* gastric cancer, *CRC* colorectal cancer

Asian populations ($P < 0.001$ and $P = 0.037$, respectively). Similarly, both cut-offs provided by Zhang et al. and Martin et al. were available for defining sarcopenia for predicting the disease-free survival ($P < 0.001$ and $P = 0.028$). In addition, preoperative sarcopenia was predive for DFS in both CRC and GC surgical patients ($P = 0.011$ and $P < 0.001$, respectively). Only one study focused on EC surgical patients, and this had no statistical significance in predicting DFS ($P = 0.235$).

Short-term outcome assessment

The forest plot of postoperative short-term complications is shown in Fig. 4 (A, total complications; B, major complications). A total of 15 studies reported 1498 postoperative complications occurring in 6489 patients and found that preoperative sarcopenia was a risk factor for total complications (RR = 1.188, 95% CI = 1.083–1.303, $P < 0.001$, $I^2 = 26.4\%$, fixed-effect model). Moreover, based on 14 studies with 526 major complications in 4204 patients, the preoperative incidence of sarcopenia was associated with a higher risk of major complications (RR = 1.228, 95% CI = 1.042–1.448, $P = 0.014$, $I^2 = 12.1\%$, fixed-effect model).

In the subgroup analysis, preoperative sarcopenia was associated with a high risk of total complications in both Asian and non-Asian populations ($P = 0.005$ and $P = 0.015$), while only a slightly significantly higher risk of major complications in Asian populations ($P = 0.049$) and no significantly higher risk in non-Asian populations were found ($P = 0.148$). Preoperative sarcopenia using cut-off provided by Zhuang et al. was a risk factor for increasing both total and major complications after surgery ($P < 0.001$ and $P = 0.001$), while there was no predictive value when using the cut-off from Prado et al. ($P > 0.05$). Sarcopenia was associated with total complications but not any major complication when using the cut-off provided by Martin et al. ($P = 0.034$ and $P = 0.946$). Preoperative sarcopenia was a risk factor in total and major complications after GC surgery ($P = 0.011$ and $P = 0.012$), but not EC surgery ($P = 0.531$ and $P = 0.169$). Sarcopenia was a risk factor for total complications after CRC surgery ($P = 0.002$), but not major complications ($P = 0.675$).

Discussion

This is the largest-scale systematic review and includes 70 studies to discuss the impact of CT-assessed sarcopenia on GI oncological patients. Our meta-analysis demonstrated that the prevalence of sarcopenia increased with the cut-off of CT-assessed SMI. Preoperative sarcopenia was associated with both long-term outcomes and short-term outcomes. More studies still need to be performed to demonstrate its efficacy in different populations, criteria and diseases.

The impact of nutrition status on oncological patients has been a research hot spot in recent years

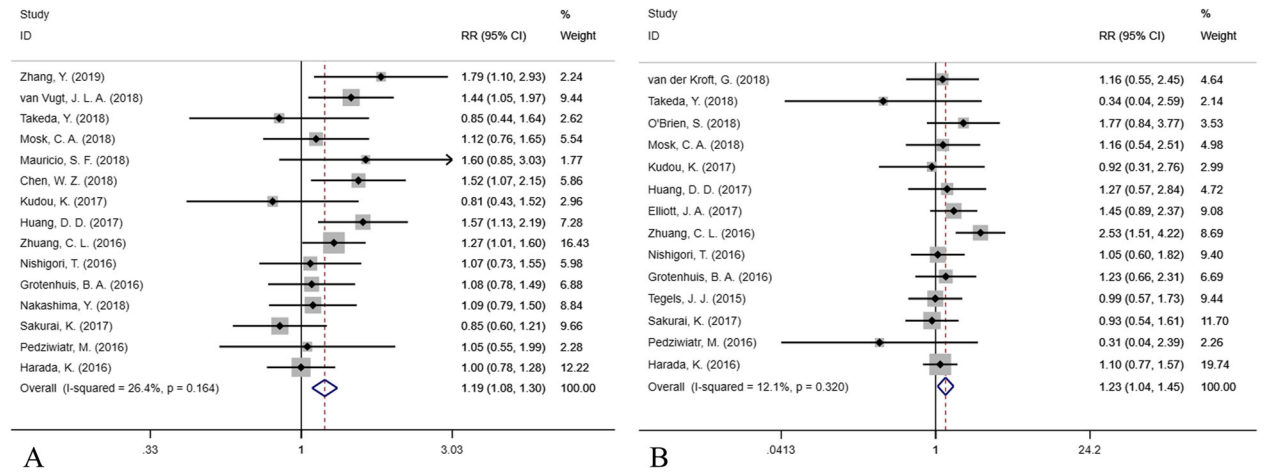

Fig. 4 The forest plot in assessing the impact of sarcopenia on short-term outcomes (**a**. total complication; **b**. major complication)

[33, 84]. Sarcopenia, defined as an age-related muscle reduction disease, has been discussed and updated over time, while the measurement and criteria still need to be determined [23, 87]. It is believed that sarcopenia is a syndrome in which the risk of adverse events is increased with a decrease in skeletal muscle mass associated with decreased muscle strength or function [87]. Because of its objectivity, repeatability, and accuracy, CT is widely used to measure muscle mass, with errors ranging from 1 to 4%, and thus it is considered a "gold standard" [69, 88]. Usually, the L3 muscle area is measured due to its accuracy reflecting the "real" muscle mass and fat volume [89]. Patients undergoing elective GI cancer surgery routinely undergo abdominal CT assessment of the patient's tumor staging without additional costs. In China, the interval between CT examination and surgery is usually used to optimize the patient's preoperative status and does not lead to delays in treatment. These optimizations include preoperative nutritional screening and support, physical functioning, pre-rehabilitation, and improvement of comorbidities [90].

Undoubtedly, the incidence of sarcopenia depends mostly on how to define the diagnostic cut-off point for sarcopenia. In our systematic review, a total 19 criteria were used to define sarcopenia. We found that the incidence of SMI was higher when the cut-off of SMI was raised. When using the Western criteria provided by Prado et al. and Martin et al., the incidence of sarcopenia was always higher for the Asian populations, which could be one heterogeneity because of the difference in body shape and diet habit [89, 91]. Although some Asian criteria were proposed, such as by Zhuang et al., Iritani et al. and Kim et al., the validation among countries still needs to be investigated for efficacy and accuracy [13, 92, 93].

Aging is a process in which all functions of the body are declining. Although current research has clarified the relationship between sarcopenia and aging, the specific primary pathogenic factors remain unclear and may be related to a series of changes caused by aging [7, 10]. The number of motor neurons in those over 70 years old is greatly reduced, and skeletal muscle mass begins to shrink at age 30 [12]. Studies have found that sarcopenia is mainly related to the decrease in the number of type II muscle fibers, which is reduced by up to 40% in patients over 70. This could explain why elders are more prone to falls [26]. In our meta-analysis, we demonstrated that preoperative sarcopenia might increase by 1.1–1.2-fold the risk of total and major complications in GI patients. Patients suffering from sarcopenia may feel weak, with limited mobility, which in turn affects the postoperative recovery process. However, until now, there was no evidence to demonstrate that preoperative increase in muscle mass could improve the outcome of GI oncological patients. One reason is that the short period during cancer diagnosis and surgery might not be enough to improve nutritional status. Most older people have insufficient protein intake or absorption barriers. Moreover, with the nutrition consumption in tumors, malnutrition and weight loss are common problems in GI malignancy patients. It not only affects hospitalization time and costs but also affects the quality of life and long-term survival of patients. Therefore, preoperative sarcopenia may be associated with postoperative complications. Early identification of the onset of sarcopenia in the elderly population and early intervention may help the patient maintain muscle mass and improve patient outcomes during treatment. Nutritional support therapy can improve the prognosis of hospitalized patients,

but there is controversy about the improvement of muscle mass and function, while exercise is beneficial in the maintenance of human physiological functions [94]. The American Cancer Society (ACS) has recommended clinical activities for all cancer patients based on clinical research on aerobic exercise and resistance training in recent decades. Age-related muscle mass and muscle strength reduction also depend on individual health status, heredity, activity function, muscle mass and muscle strength training, and nutritional levels [12]. Patients with sedentary movements have a more pronounced decrease in the number and intensity of muscle fibers compared with patients with normal activities, revealing that exercise can slow muscle atrophy. Active exercise combined with essential amino acid nutrition support can improve muscle status and is an effective way to fight muscle deficiency [95].

Most studies currently focus only on the relationship between sarcopenia and clinical outcomes and rarely explore the causes. Studies have found that muscle reduction reflects an increase in the metabolism of malignant tumors, resulting in an increased systemic inflammatory response and increased muscle consumption [96]. Moreover, several studies found that a systemic inflammatory response significantly increased the adverse outcomes of patients [97, 98]. Richards et al. found a clear correlation between muscle reduction in patients with resectable primary CRC and systemic inflammatory response [97]. Aleman et al. suggested that inflammatory cells may participate in the onset of sarcopenia by interfering with the skeletal muscle insulin-like growth factor-I pathway [98]. This may explain why the poor prognosis in sarcopenia may be related to an increase in the systemic inflammatory response. Sarcopenia may also be affected by genetic factors. A genome-wide association study found that genes associated with sarcopenia and osteoporosis include growth differentiation factor 8, myocyte enhancer factor 2C, and peroxisome proliferator receptor gamma coactivator 1a. There are currently few reports on the genetics of sarcopenia, and further research is still needed [99].

There were some limitations to our study. First, due to the observational nature of the available studies, the evidence was “low quality” by the GRADE criteria. More prospective randomized control trials need to be performed to investigate the efficacy of sarcopenia in predicting outcomes in oncological patients. Second, due to the heterogeneity existing due to the different cut-offs and diseases, the included studies had few subgroup analyses. Third, the Clavien-Dindo classification is suitable for assessing postoperative complications, while sarcopenia may be associated with some specific complications, such as respiratory complications, infectious complications and postoperative leakage, which could not be calculated in every included study. Further efforts need to be made in individual patient meta-analyses and regressions to discuss the risk of sarcopenia in oncological patients.

Conclusion

The prevalence of sarcopenia increases when the cut-off of SMI increases. The preoperative incidence of sarcopenia is a risk factor for both overall and disease-free survival and short-term total and major postoperative complications in the whole population of gastrointestinal oncology patients. In the subgroup analysis, sarcopenia is related to higher complication, recurrence and mortality rates in CRC and GC surgical patients. The cut-off provided by Martin et al. is the most common predictable criteria globally, while more Western cohorts need to be validated when using cut-offs provided by Asian countries.

Abbreviations

CI: Confidence interval; CRC: Colorectal cancer; CT: Computed tomography; DFS: Disease-free survival; EC: Esophageal cancer; GC: Gastric cancer; GI: Gastrointestinal; GRADE: The grading of recommendations, assessment, development, and evaluation; HR: Hazard ratio; L3: The third lumbar; OS: Overall survival; PRISMA: Preferred reporting items for systematic review and meta-analysis; RR: Relative risk; SMI: Skeletal muscle index; TPA: Total psoas area; VFA: Visceral fat area; VFV: Visceral fat volume

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Authors’ contributions

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Competing interests

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