### **REVIEW ARTICLE**



# Effect of sarcopenia on clinical outcomes following digestive carcinoma surgery: a meta-analysis

Hongxia Hua<sup>1</sup> • Xinyi Xu<sup>1</sup> • Yu Tang<sup>2</sup> • Ziqi Ren<sup>1</sup> • Qin Xu<sup>1</sup> • Li Chen<sup>3</sup>

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### Abstract

**Background** The effect of sarcopenia on digestive carcinoma surgery outcomes is controversial. We aimed to assess the effect of sarcopenia defined by the European Working Group on Sarcopenia in Older People (EWGSOP) or the Asian Working Group for Sarcopenia (AWGS) on outcomes following digestive carcinoma surgery.

**Methods** Eligible studies were searched from PubMed, EMBASE and other databases from inception to April 2018. We conducted a meta-analysis to estimate the risk ratios or mean differences of outcomes in the sarcopenia group versus the non-sarcopenia group. Stratified analyses and sensitivity analyses were performed.

**Results** We included 11 cohort studies, with a sarcopenia prevalence ranging from 11.6 to 33.0%. Sarcopenia was associated with an increased risk of total complications (RR = 1.87, P < 0.00001), major complications (RR = 2.45, P = 0.002), re-admissions (RR = 2.53,P < 0.0001), infections (RR = 2.23, P = 0.09), severe infections (RR = 2.96, P = 0.04), 30-day mortality (RR = 3.36, P = 0.001), longer hospital stay (MD = 4.61, P = 0.001) and increased hospitalization expenditures (SMD = 0.25, P = 0.02). Sarcopenia differentially affected outcomes when stratified, and the results were stable.

**Conclusions** Sarcopenia defined by the EWGSOP or AWGS Consensus was a high-risk factor for digestive carcinoma surgery outcomes. Different tumour site and muscle mass measurements are the sources of heterogeneity. More high-quality studies are needed.

Keywords Sarcopenia · Digestive carcinoma · Surgery · Clinical outcomes

# Introduction

Digestive carcinomas mainly fall into gastric, colorectal, esophageal and liver types. According to the global estimation of cancer incidence and mortality in 2018 announced by International Agency for Research on Cancer (IARC), new cases of digestive carcinoma accounted for 16.8% of the total new cancers and digestive cancer-related deaths 35.4% of the total [1]. Currently, surgery is still the main therapeutic

Hongxia Hua and Xinyi Xu contributed equally to this work.

☑ Qin Xu 248629512@qq.com

- <sup>1</sup> School of Nursing, Nanjing Medical University, Nanjing 211166, China
- <sup>2</sup> Department of Thoracic Surgery, the First Affiliated Hospital of Nanjing Medical University, Nanjing 211166, China
- <sup>3</sup> Department of General Surgery, the First Affiliated Hospital of Nanjing Medical University, Nanjing 211166, China

method; however, due to the limitation of early diagnosis and treatment, digestive carcinomas have higher mortality than other neoplasms [2, 3]. Since the aging problem is getting so serious that senior citizens will account for 22% of all population in the world until 2050, the incidence of digestive carcinoma is higher among the elderly [4]. Studies have shown that the complication rate, mortality and length of hospital stay after digestive carcinoma surgery increase with patient age [5, 6].

Sarcopenia was first put forward by Irwin Rosenberg in 1989 and defined as an age-related loss of skeletal muscle mass [7]. It has been found that focussing solely on skeletal muscle mass may limit clinical applications. Muscle mass has a non-linear relationship with muscle strength [8], and the loss of muscle strength also has important clinical significance. For this reason, the 2010 EWGSOP Consensus [9] and the 2014 AWGS Consensus [10] defined sarcopenia as a syndrome characterized by a progressive and generalized loss of skeletal muscle mass and strength with a risk of adverse outcomes, such as physical disability, poor quality of life and death. Several studies have

shown that sarcopenia may increase the risk of postoperative complications and thus reduce the survival rate of patients undergoing digestive carcinoma surgery [11, 12].

Sarcopenia always occurs as part of the aging process [13, 14], muscle loss starts at 30 years of age and accelerates after 70 years [15] and the prevalence of sarcopenia is  $5\sim13\%$  in people aged from 60 to 70 years old as well as  $11\sim50\%$  in people aged over 80 years [16]. Sarcopenia is also related to malnutrition, disuse, surgery, cancer, chronic diseases and so on [17–20]. The characteristics of elderly patients undergoing digestive carcinoma surgery are consistent with the main causes of sarcopenia such as aging, malnutrition and cancer. Therefore, the prevalence of sarcopenia in elderly patients undergoing digestive carcinoma surgery is higher than that in the general population, varying from 11.1 to 76% [21].

To improve the poor prognosis, therefore, we should pay more attention to such related risk factors as sarcopenia. Although the EWGSOP and AWGS Consensus have updated the definition of sarcopenia, most of studies still confine sarcopenia to the loss of muscle mass, ignoring the decline of muscle strength and function [22-25]. The effect of sarcopenia on clinical outcomes is controversial among studies using different definitions of sarcopenia. For example, one study [26] concluded that sarcopenia defined by AWGS Consensus was only related to postoperative complications but not to readmissions, hospital stay and mortality. But another study [24] showed that sarcopenia, defined as the loss of muscle mass, was related to a higher risk of longer hospital stay. Recently, several meta-analyses [21, 27] aimed to find a relationship between sarcopenia and clinical outcomes, but these studies included articles that define sarcopenia using different criteria, which may have resulted in some bias and great heterogeneity. A related meta-analysis [28] paid attention to this aspect and conducted a subgroup analysis stratified by the different definitions of sarcopenia, suggesting that studies using the EWGSOP definition had higher relative risks associated with sarcopenia and less heterogeneity. However, that analysis, only with three studies based on the EWGSOP Consensus definition, also had high heterogeneity and focused only on postoperative complications. We found that the effect of sarcopenia on outcomes is also controversial among studies using the EWGSOP or AWGS Consensus definition [12, 29].

Therefore, our study aimed to further assess the effect of sarcopenia just defined by the EWGSOP or AWGS Consensus on clinical outcomes in elderly patients undergoing digestive carcinoma surgery.

# Methods

The Preferred Reporting Items for Systematic Review and Meta-Analyses guidelines were followed when we conducted and reported this systematic review [30].

#### Literature search

The PubMed, Web of Science, EMBASE, Cochrane Library, Science Direct, CNKI, and WanFang databases were searched from inception to April 2018. The search strategy keywords and the medical subject headings (MeSH) used included digestive carcinoma, surgery, and sarcopenia. Reference lists of all relevant systematic reviews were searched to identify additional studies. The literature search was conducted by one author, who had received systematic training. The languages of the literature were limited to English and Chinese.

## **Eligibility criteria**

We included clinical studies that met these criteria: (1) only observational studies; (2) studies investigating the effects of sarcopenia on clinical outcomes; (3) the target patients were aged 60 years or older with digestive carcinoma and received surgical treatment; (4) considering there are different definitions of sarcopenia (Box 1), we just included studies that defined sarcopenia by the EWGSOP or AWGS Consensus; and (5) the end points of interest included at least one of the following characteristics: total complications, major complications, infections, severe infections, re-admissions, 30-day mortality, hospital stay and hospitalization expenditures. We excluded meeting proceedings, letters, reviews, commentary and grey literature.

Box 1 The definitions of sarcopenia

Irwin Rosenberg(1989)	EWGSOP Consensus
	(2010)/AWGS
I ago of chalated muscule	Loss of sheletel muscle mose
mass	and strength or physical function
	Irwin Rosenberg(1989) Loss of skeletal muscle mass

### **Data extraction**

Two researchers independently extracted the data and any disagreements were resolved via consensus. We extracted the first author's last name, publication year, country, study type, sample size, sex proportion, tumour site, measurements cut-off value for sarcopenia and the postoperative outcomes, including total complications, major complications, infections, severe infections, re-admissions and 30-day mortality after surgery, hospital stay and hospitalization expenditures. We defined postoperative complications using the Clavien-Dindo classification as follows [31]: "total complications" were equal to "Clavien-Dindo grade  $\geq 2$ ", and "major complications" were equal to "Clavien-Dindo grade  $\geq 3$ ". If

insufficient information was available, then the authors were contacted via e-mail.

### **Quality assessment**

Risk of bias was assessed by two researchers independently using the Newcastle–Ottawa Scale (NOS) [32]. A score equal to or less than 5 was considered as low quality, 6 or 7 as moderate and 8 or 9 as high. Any disagreements were resolved through consensus.

### **Statistical analysis**

The meta-analysis was undertaken using Review Manager (RevMan V.5.3; Cochrane Collaboration, Oxford, UK) when more than two studies reported the same outcome with a significance level of 0.05 [33]. We pooled the risk ratios (RRs) or mean differences (MDs) for dichotomous or continuous variables using a fixed or random effects model as appropriate. The  $I^2$  statistic was used to quantify statistical heterogeneity. The fixed effects model was used when  $I^2 \leq 30\%$ , and a random effects model was used when  $I^2 > 30\%$ . Subgroup analyses were performed to investigate the origin of the heterogeneity [34]. We performed stratified analyses according to the muscle mass measurements and tumour site to investigate the effect modifications of these variables on the association between sarcopenia and the risk of clinical outcomes. Then, we conducted sensitivity analyses to test the robustness.

# Results

# Search results

From a total of 10,226 records identified following a detailed search, 11 studies [11, 12, 26, 29, 35–41] with 2419 participants were finally included (Fig. 1). Of these studies, two were retrospective cohort studies [11, 29], and the others were prospective cohort studies. One study focused on colorectal cancer patients [26], six focused on gastric cancer patients [12, 29, 36, 38, 39, 41], two focused on esophageal cancer patients [11, 40] and two focused on liver cancer patients undergoing liver transplantation [35, 37]. The characteristics of the included studies are shown in Table 2.

### **Quality assessment**

The quality assessments of the 11 included studies are summarized in Table 3. Of these studies, four were graded as high quality [12, 26, 35, 41], six as moderate [11, 36–40] and one as low [29].

### Relationship between sarcopenia and complications

Eight studies [12, 26, 29, 35, 36, 38, 39, 41] reported an association of sarcopenia with total complications. One study was excluded due to loss of data [36]. We calculated the summary RR value using a random effects model, which suggested that sarcopenia was associated with an increased risk of total complications, with a pooled RR of 1.87 (95% CI 1.52–2.30). High heterogeneity was found across these



studies ( $\chi^2 = 10.74$ , P = 0.10,  $I^2 = 44\%$ ) (Fig. 2a). The pooled results from the four studies focused on major complications [12, 26, 29, 41] that suggested that sarcopenia was associated with an increased risk of major complications (RR = 2.45, 95% *CI* 1.38–4.32). No significant heterogeneity was observed across these four studies ( $\chi^2 = 2.18$ , P = 0.53,  $I^2 = 0\%$ ) (Fig. 2b).

### Relationship between sarcopenia and re-admissions

Five studies [12, 26, 39–41] reported a relation of sarcopenia to re-admissions. The pooled results from these five studies showed that sarcopenia was associated with an increased risk of re-admission (RR = 2.53, 95% *CI* 1.66–3.85). No significant heterogeneity was found among the studies ( $\chi^2$  = 2.09, P = 0.72,  $I^2$  = 0%) (Fig. 2c).

### Relationship between sarcopenia and infections

Five studies [12, 26, 29, 40, 41] focused on patients' postoperative infections, such as surgical site infections and pneumonia. The results showed that sarcopenia was associated with an increased risk of infections (RR = 2.23, 95% *CI* 1.23–4.03) in the random effects model due to relatively high heterogeneity ( $\chi^2 = 8.16$ , P = 0.09,  $I^2 = 51\%$ ) (Fig. 2d). Two studies [29, 35] reported an association between sarcopenia and severe infections with a CD grade of IIIa or higher. The analyses showed that sarcopenia conferred a higher risk of severe infections, with a pooled RR of 2.96 (95% *CI* 1.04– 8.46) in the fixed effects model due to a lack of heterogeneity ( $\chi^2 = 0.57$ , P = 0.45,  $I^2 = 0\%$ ) (Fig. 2e).

 Table 1
 Main characteristics of the included studies

# Relationship between sarcopenia and 30-day mortality

Three studies [35, 37, 41] observed 30-day mortality. We combined the 30-day mortality data using a fixed effects model given the relatively low heterogeneity ( $\chi^2 = 2.63$ , P = 0.27,  $I^2 = 24\%$ ). The results showed that sarcopenia was associated with an increased risk of 30-day mortality, with a pooled RR of 3.36 (95% *CI* 1.60–7.06) (Fig. 2f).

# Relationship between sarcopenia and the length of the hospital stay

Nine studies [11, 12, 26, 29, 35, 38, 39, 41] focused on sarcopenia and the length of the hospital stay. We calculated the mean difference using a random effects model due to the high heterogeneity ( $\chi^2 = 23.12$ , P = 0.003,  $I^2 = 65\%$ ). The results showed that sarcopenia was associated with a longer postoperative hospital stay, with a mean difference of 4.61 (95% *CI* 1.84–7.39) (Fig. 2g).

# Relationship between sarcopenia and hospitalization expenditures

Two studies [39, 41] reported an association between sarcopenia and hospitalization expenditures. In the fixed effects model, sarcopenia was associated with more hospitalization expenditures, with a standardized mean difference of 0.25 (95% *CI* 0.04–0.46). No significant heterogeneity was found between the studies ( $\chi^2 = 0.11$ , P = 0.74,  $I^2 = 0\%$ ) (Fig. 2h).

No.	Author, year	Country	Design	Sample (M/F)	Prevalence (%)	Tumour site	Measurements
1	Huang 2015	China	Prospective	142 (88/54)	12	Colorectal	L3 SMI CT <sup>a</sup> , GS <sup>a</sup> , GP <sup>a</sup>
2	Ma 2018	China	Prospective	184 (152/32)	33	Gastric	L3 SMI CT <sup>a</sup> , GS <sup>a</sup> , GP <sup>a</sup>
3	Huang 2016	China	Prospective	173 (135/38)	30	Gastric	L3 SMI CT <sup>b</sup> , GS <sup>a</sup> , GP <sup>a</sup>
4	Zhou 2017	China	Prospective	240 (190/50)	29	Gastric	L3 SMI CT <sup>b</sup> , GS <sup>a</sup> , GP <sup>a</sup>
5	Fukuda 2016	Japan	Retrospective	99 (66/33)	21	Gastric	SMI BIA <sup>a</sup> , GS <sup>b</sup> , GP <sup>a</sup>
6	Wang 2016	China	Prospective	255 (190/65)	13	Gastric	L3 SMI CT <sup>a</sup> , GS <sup>a</sup> , GP <sup>a</sup>
7	Kawamura 2018	Japan	Prospective	951 (660/291)	12	Gastric	AMA <sup>a</sup> AM, GS <sup>a</sup>
8	Makiura 2016	Japan	Retrospective	104 (88/16)	28	Oesophageal	ASMMI BIA <sup>b</sup> , GS <sup>a</sup> , GP <sup>a</sup>
9	Makiura 2018	Japan	Prospective	98 (83/15)	32	Oesophageal	ASMMI BIA <sup>b</sup> , GS <sup>a</sup> , GP <sup>a</sup>
10	Harimoto 2017	Japan	Prospective	101 (45/56)	24	Liver	L3 SMI CT <sup>c</sup> , GS <sup>a</sup> , GP <sup>a</sup>
11	Kaido 2016	Japan	Prospective	72 (-/-)	14	Liver	ASMMI BIA <sup>c</sup> , GS <sup>a</sup>

*L3 CT* third lumbar vertebra computed tomography scan, *SMI* skeletal muscle index, *BIA* bioelectrical impedance, *ASMMI* appendicular skeletal muscle mass index, *AM* anthropometric measurement, *AMA* arm muscle area, *GS* grip strength, *GP* gait speed,  $CT^a \text{ men} < 36.0 \text{ cm}^2/\text{m}^2$ , women  $< 29.0 \text{ cm}^2/\text{m}^2$ ,  $CT^b \text{ men} < 40.8 \text{ cm}^2/\text{m}^2$ , women  $< 34.9 \text{ cm}^2/\text{m}^2$ ,  $CT^e < 75\%$  of the standard, *AMA*<sup>a</sup> men  $< 38.05 \text{ cm}^2$ , women  $< 27.87 \text{ cm}^2$ , *BIA*<sup>a</sup> men  $< 8.87 \text{ kg/m}^2$ , women  $< 6.42 \text{ kg/m}^2$ , *BIA*<sup>b</sup> men  $< 7.0 \text{ kg/m}^2$ , women  $< 5.7 \text{ kg/m}^2$ , *BIA*<sup>c</sup> < 90% of the lower limit of the standard, *GS*<sup>a</sup> men < 26, women < 18, *GS*<sup>b</sup> men < 30, women < 18, *GP*<sup>a</sup> gait speed < 0.8 m/s

No.	Group	Mortality	Re-admissions	Total complications	Major complications	Infections	Severe infections	Hospital stay (days)	Costs (¥)
1	Sarcopenia	_	2	10	2	7	_	$15\pm10.50$	_
	Non-	-	4	30	3	2	-	$13\pm 6$	-
2	Sarcopenia	-	9	26	_	_	-	$16.5\pm11$	$67,\!117.8\pm30,\!057.4$
	Non-	-	4	36	_	_	-	$14\pm 6$	61,523.7±24,777.6
3	Sarcopenia	16 <sup>a</sup>	_	_	_	-	_	-	_
	Non-	$8^{a}$	_	_	_	-	_	-	_
4	Sarcopenia	$0^{\mathrm{b}}$	6	34	6	10	_	$16\pm9$	$65,\!973.1 \pm 28,\!789$
	Non-	$1^{b}$	9	42	10	7	_	$13\pm 6$	$59,229.5 \pm 21,890$
5	Sarcopenia	-	_	12	6	3	2	18 (4–104)	_
	Non-	_	_	28	7	14	4	16 (9–152)	_
6	Sarcopenia	-	6	14	3	6	_	$16 \pm 14.25$	_
	Non-	-	18	32	6	8	_	$13\pm7$	_
7	Sarcopenia	-	_	56	_	-	_	$12\pm23.3$	_
	Non-	-	_	286	_	-	_	$10\pm14.6$	_
8	Sarcopenia	-	_	_	_	-	_	53 (32-80)	_
	Non-	-	_	_	_	-	_	28 (23-41)	_
9	Sarcopenia	-	12	_	_	5	-	53 (33–78)	_
	Non-	-	11	_	_	10	_	30 (23-41)	_
10	Sarcopenia	6 <sup>b</sup>	_	10	_	_	4	$44\pm27$	_
	Non-	7 <sup>b</sup>	_	14	_	-	3	$31\pm23$	_
11	Sarcopenia	4 <sup>b</sup>	_	_	_	-	-	-	_
	Non-	3 <sup>b</sup>	_	_	_	_	_	_	-

The data in this table represent the number of patients. Except for special annotations, such as length of hospital stay and hospitalization expenditures, the data are expressed as the mean  $\pm$  standard deviation or median (interquartile range)

<sup>a</sup> Mean 1-year mortality

<sup>b</sup> Mean 30-day mortality

# Subgroup analyses

We did subgroup analyses according to the muscle mass measurements and tumour site. Results are shown in Table 4.

# Discussion

In our study, the prevalence of sarcopenia varied from 11.6 to 33% in the included studies, which was lower than that of other studies because our included studies defined sarcopenia based only on the EWGSOP or AWGS Consensus. The prevalence of sarcopenia was 18.14% for gastric, 11.9% for colorectal, 29.7% for esophageal, and 19.7% for liver cancer patients. We infer that the reason for the higher prevalence of sarcopenia in oesophageal cancer patients might be related to the inadequate intake of energy and proteins caused by progressive dysphagia.

The pathology of sarcopenia is complex and can include specific nutritional deficiencies [42], a lack of physical activity [43], insulin resistance [44] and chronic inflammation [45].

Sarcopenia may also result in a decline in the metabolic rate and aerobic capacity and an increased risk of physical

 
 Table 3
 The Newcastle–Ottawa Scale for assessment of the quality of the included studies

No.	Sele	ection			Comp	arability	Out	come	Total score	
	(1)	(2)	(3)	(4)	(1a)	(1b)	(1)	(2)	(3)	
1	1	1	1	1	1	1	1	1	0	8
2	1	1	1	1	1	0	0	1	0	6
3	1	1	1	1	1	0	0	1	1	7
4	1	1	1	1	1	1	1	1	0	8
5	1	1	1	1	1	0	0	0	0	5
6	1	1	1	1	1	0	1	1	1	8
7	1	1	1	1	1	1	1	0	0	7
8	1	1	1	1	1	0	0	1	0	6
9	1	1	1	1	1	0	0	1	0	6
10	1	1	1	1	1	1	1	1	0	8
11	1	1	1	1	1	1	0	1	0	7

Fig. 2 Summary results of the clinical outcomes for subjects with sarcopenia versus those without sarcopenia. **a** Total complications. **b** Major complications. **c** Re-admissions. **d** Infections. **e** Severe infections. **f** Thirty-day mortality. **g** The length of the hospital stay

# a Total complications

	sarcop	enia	nonsarco	penia		Risk Ratio	Risk Ratio				
Study or Subgroup	Events Total		Events	Total	Weight	M-H. Random, 95% C		M-H, Ran	dom. 95% C		
Fukuda 2016	12	21	28	78	12.2%	1.59 [0.99, 2.56]			-		
Harimoto 2017	10	24	14	77	7.5%	2.29 [1.17, 4.48]					
Huang 2015	10	17	30	125	11.3%	2.45 [1.48, 4.06]					
Kawamura 2018	56	111	286	840	25.7%	1.48 [1.20, 1.82]			-		
MA 2018	26	60	36	124	15.1%	1.49 [1.00, 2.23]			-		
Wang 2016	14	32	32	223	11.2%	3.05 [1.84, 5.06]			-		
Zhou 2017	34	69	42	171	17.1%	2.01 [1.41, 2.86]					
Total (95% CI)		334		1638	100.0%	1.87 [1.52, 2.30]			•		
Total events	162		468								
Heterogeneity: Tau <sup>2</sup> =	0.03; Chi2	= 10.74	4, df = 6 (P	= 0.10);	l <sup>2</sup> = 44%		+	-	1	1	-+
Test for overall effect:	Z = 5.93 (	P < 0.00	0001)				0.02	sarcopenia	nonsarcop	enia	50

# b Major complications

	sarcopenia nonsarcope			enia		Risk Ratio	Risk Ratio			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C		M-H. Fixed, 95% CI		
Fukuda 2016	6	21	7	78	27.1%	3.18 [1.20, 8.47]				
Huang 2015	2	17	3	125	6.6%	4.90 [0.88, 27.26]			_	
Wang 2016	3	32	6	223	13.8%	3.48 [0.92, 13.25]				
Zhou 2017	6	69	10	171	52.5%	1.49 [0.56, 3.93]				
Total (95% CI)		139		597	100.0%	2.45 [1.38, 4.32]		•		
Total events	17		26							
Heterogeneity: Chi2 = :	0.53); l <sup>2</sup> = 0%				+					
Test for overall effect:	Z = 3.08 (I	P = 0.0	02)				0.02	sarcopenia nonsarcopenia	50	

# c Re-admissions

	sarcop	nonsarcop	enia		Risk Ratio	Risk Ratio				
Study or Subgroup Events		Total	Events	Total	Weight	M-H. Fixed, 95% C		M-H, Fix	ed. 95% Cl	
Huang 2015	2	17	4	125	4.7%	3.68 [0.73, 18.58]		-		
MA 2018	9	60	4	124	12.9%	4.65 [1.49, 14.49]				-
Makiura 2018	12	31	11	67	34.4%	2.36 [1.17, 4.74]				
Wang 2016	6	32	18	223	22.3%	2.32 [1.00, 5.42]				
Zhou 2017	6	69	9	171	25.6%	1.65 [0.61, 4.47]		-	-	
Total (95% CI)		209		710	100.0%	2.53 [1.66, 3.85]			•	
Total events	35		46							
Heterogeneity: Chi <sup>2</sup> = 2	2.09, df = 4	4 (P = 0	0.72); l <sup>2</sup> = 0%				+			1
Test for overall effect:	001)			0.02	sarcopenia	nonsarcopeni	a 50			

# d Infections

	sarcop	enia	nonsarcopenia			Risk Ratio		Risk Ratio			
Study or Subgroup	Events	Events Total Ev		Total	Weight	M-H, Random, 95% C		M-H, Random, 95% CI			
Fukuda 2016	3	21	14	78	15.9%	0.80 [0.25, 2.51]			-		
Huang 2015	7	17	22	125	26.0%	2.34 [1.18, 4.63]					
Makiura 2018	5	29	10	75	19.0%	1.29 [0.48, 3.46]			-		
Wang 2016	6	32	8	223	18.8%	5.23 [1.94, 14.09]					
Zhou 2017	10	69	7	171	20.2%	3.54 [1.40, 8.92]					
Total (95% CI)		168		672	100.0%	2.23 [1.23, 4.03]			•		
Total events	31		61								
Heterogeneity: Tau <sup>2</sup> =	0.23; Chi <sup>2</sup>	= 8.16	df = 4 (P =	0.09); 12	= 51%		+				
Test for overall effect:	Z = 2.65 (I	P = 0.0	08)			0.02	0.1 sarcopenia	nonsarcopenia	50		

# e Severe infections

	sarcop	enia	nonsarcop	enia		Risk Ratio	Risk Ratio			
Study or Subgroup	roup Events Total I			Total	Weight	M-H. Fixed, 95% C	I	M-H, Fix	red. 95% CI	
Fukuda 2016	2	21	4	78	54.3%	1.86 [0.36, 9.46]				
Harimoto 2017	4	24	3	77	45.7%	4.28 [1.03, 17.79]			-	·
Total (95% CI)		45		155	100.0%	2.96 [1.04, 8.46]			-	
Total events	6		7							
Heterogeneity: Chi <sup>2</sup> = 0.57, df = 1 (P = 0.45); l <sup>2</sup> = 0%							+	0.1		
Test for overall effect:	Z = 2.03 (	P = 0.0	4)				0.02	sarcopenia	nonsarcopenia	50

# f 30-d mortality

	sarcop	enia	nonsarco	penia		<b>Risk Ratio</b>	Risk Ratio				
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C		М-Н.	Fixed, 95	% CI	
Harimoto 2017	6	24	7	78	65.9%	2.79 [1.04, 7.50]					
Kaido 2016	4	10	3	62	16.7%	8.27 [2.17, 31.56]			1 1		_
Zhou 2017	0	69	1	171	17.4%	0.82 [0.03, 19.86]	-		•		
Total (95% CI)		103		311	100.0%	3.36 [1.60, 7.06]				•	
Total events	10		11								
Heterogeneity: Chi <sup>2</sup> = 2	0.27); l <sup>2</sup> = 24	%			0.02	0.1	1	10	50		
Test for overall effect: 2	Z = 3.20 (	P = 0.0	01)				0.02	sarcoper	nia nons	sarcopenia	50

# g The length of the hospital stay

sarco		copeni	a	nons	arcope	nia		Mean Difference		ifference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV. Random, 95% C		IV, Rand	om. 95% CI	
Fukuda 2016	28	26.46	21	24	29.76	78	3.7%	4.00 [-9.10, 17.10]				
Harimoto 2017	44	27	24	31	27	77	4.1%	13.00 [0.63, 25.37]			<u> </u>	
Huang 2015	15	7.78	17	13	4.44	125	15.9%	2.00 [-1.78, 5.78]			-	
Kawamura 2018	12	23.3	111	10	14.6	840	14.3%	2.00 [-2.45, 6.45]			<b>•</b>	
MA 2018	16.5	8.15	60	14	4.44	124	19.7%	2.50 [0.29, 4.71]			+	
Makiura 2016	55	37.42	29	30	13.61	75	3.4%	25.00 [11.04, 38.96]				-
Makiura 2018	55	34.97	31	31	13.64	67	3.9%	24.00 [11.26, 36.74]				
Wang 2016	16	10.56	32	13	5.19	223	16.0%	3.00 [-0.72, 6.72]			-	
Zhou 2017	16	10.35	69	13	4.44	171	19.0%	3.00 [0.47, 5.53]			-	
Total (95% CI)			394			1780	100.0%	4.61 [1.84, 7.39]			•	
Heterogeneity: Tau <sup>2</sup> =	8.93; Ch	ni² = 23.	12, df =	= 8 (P =	0.003);	$l^2 = 65$	%		+			
Test for overall effect:	Z = 3.26	6 (P = 0.	001)						-50	-25 sarcopenia	nonsarcopenia	50

# h Hospitalization expenditures

	sarcopenia			nonsarcopenia			Std. Mean Difference		Std. Mean Difference				
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI		IV, Fi	xed,	. 95% CI	
MA 2018	67,117.8	30,057.4	60	61,523.7	24,777.6	124	45.2%	0.21 [-0.10, 0.52]		-	-	-	
Zhou 2017	65,973.1	28,789	69	59,229.5	21,890	171	54.8%	0.28 [-0.00, 0.56]			h		
Total (95% CI)			129			295	100.0%	0.25 [0.04, 0.46]				-	-
Heterogeneity: Chi <sup>2</sup> = Test for overall effect:	0.11, df = 1 Z = 2.34 (F	(P = 0.74) = 0.02)	; l <sup>2</sup> = 0 <sup>4</sup>	16					-0.5	-0.25 sarcopen	0 ia i	0.25 nonsarcopenia	0.5

disability, poor quality of life and death [46, 47]. The prognosis of digestive carcinoma surgery is unfavourable; thus, enhanced recovery after surgery, advanced surgical techniques, perioperative nursing and preoperative risk assessments have received more attention as a way to improve the prognosis. Currently, preoperative risk assessments include the American Society of Anaesthesiologists classification, nutritional risk screening and a preoperative routine examination. However, these indicators are not accurate. The guidelines from the American College of Surgeons also highlighted the importance of assessing sarcopenia prior to oncologic surgery in the elderly [48]. Recently, some articles have investigated the association between sarcopenia and the risk of adverse outcomes following digestive carcinoma surgery, although the conclusions are controversial. To the best of our knowledge, our meta-analysis is the first to investigate the relationships between sarcopenia defined by the EWGSOP or AWGS Consensus and outcomes after surgery for digestive carcinoma. Our meta-analysis showed that sarcopenia was associated with a high risk of worse clinical outcomes, including total complications, major complications, re-admissions, infections, severe infections, 30-day mortality, hospital stay and hospitalization expenditures. These results suggest that we should add sarcopenia to preoperative risk assessments and construct a surgical risk prediction model. Clinicians need to analyse risk factors for sarcopenia in patients who plan to undergo digestive carcinoma surgery and then formulate interventions for specific disease and nutritional statuses based on the risk factors to alleviate adverse postoperative outcomes.

The heterogeneity of our meta-analysis was low, except for total complications, infections and lengths of hospital stay. Subgroup analyses showed that sarcopenia remained a highrisk factor for re-admissions across muscle mass measurements, whereas different effect results were found for total complications, infections and lengths of hospital stay in the different subgroups. Currently, many methods for muscle

#### Table 4 Results of subgroup analyses

Clinical	Muscle mass measurements		Tumour site			
outcomes	RRs/MD	Heterogeneity	RRs/MD	Heterogeneity		
Total	CT subgroup:	Significant	Gastric cancer subgroup:	No significant		
complications	RR = 2.11 (95% <i>CI</i> 1.66–2.69)	$(\chi^2 = 4.82, P = 0.09, I^2 = 58.5\%)$	RR = 1.77 (95% <i>CI</i> 1.40–2.23)	$(\chi^2 = 1.64, P = 0.44, I^2 = 0\%)$		
	BIA subgroup: RR = 1.59 (95% <i>CI</i> 0.99–2.56) AM subgroup: RR = 1.48 (95% <i>CI</i> 1.20–1.82)		Liver cancer subgroup: RR = 2.29 (95% <i>CI</i> 1.17–4.48) Colorectal cancer subgroup: RR = 2.45 (95% <i>CI</i> 1.48–4.06)			
Re-admissions	CT subgroup:	No significant	Gastric cancer subgroup:	No significant		
	RR = 2.62 (95% <i>CI</i> 1.55–4.43)	$(\chi^2 = 0.05, P = 0.82, I^2 = 0\%)$	RR = 2.53, 95% CI 1.45–4.42	$(\chi^2 = 0.24, P = 0.89, I^2 = 0\%)$		
	BIA subgroup: RR = 2.36 (95% CI 1.17–4.74)		Esophageal cancer subgroup: RR = 2.36, 95% <i>CI</i> 1.17–4.74 Colorectal cancer subgroup: RR = 3.68, 95% <i>CI</i> 0.73–18.58			
Infections	CT subgroup:	Significant	Gastric cancer subgroup:	No significant		
	RR = 3.16 (95% <i>CI</i> 1.95–5.11)	$(\chi^2 = 5.87, P = 0.02, I^2 = 83\%)$	RR = 2.55, 95% CI 0.88–7.37	$(\chi^2 = 1.15, P = 0.56, I^2 = 0\%)$		
	BIA subgroup:		Esophageal cancer subgroup:			
	RR = 1.05 (95% CI 0.50–2.22)		RR = 1.29, 95% CI 0.48-3.46			
			Colorectal cancer subgroup:			
			RR = 2.34, 95% CI 1.18-4.63			
Length of hospital stay	CT subgroup:	Significant	Gastric cancer subgroup:	Significant		
	MD = 2.79 (95% <i>CI</i> 1.39–4.19)	$(\chi^2 = 4.76, P = 0.09, I^2 = 58\%)$	MD = 2.83, 95% <i>CI</i> 1.42–4.25	$(\chi^2 = 20.24, P < 0.0001, I^2 = 90.1\%)$		
	BIA subgroup MD = 17.60 (95% CI 4.14–31.07)		Esophageal cancer subgroup: MD = 24.45, 95% <i>CI</i> 15.04–33.86			
	AM subgroup:		Colorectal cancer subgroup:			
	MD = 2.00 (95% <i>CI</i> - 2.45–6.45)		MD = 2.00, 95% CI - 1.78–5.78			

AM mean anthropometric measurements

mass measurement have been developed, including dual Xray absorptiometry (DXA), BIA, sonography, magnetic resonance imaging (MRI) and CT. CT is the gold standard and has become part of preoperative investigations in patients with abdominal carcinoma. BIA, DXA and skinfold measurements are not performed routinely during oncological evaluations, but these measurements also have their own advantages. In this meta-analysis, we found that sarcopenia significantly affected all outcomes in the CT subgroup, so the lack of a uniform muscle mass assessment methodology might have affected the study outcomes. We also found that the source of heterogeneity in total complications and infections was the muscle mass measurements. Thus, clinical trials need to compare other muscle mass measurements with CT and recommend the best method for different races and illnesses to narrow measurement error in the future. When stratified by tumour site, sarcopenia remained a high-risk factor for total complications regardless of tumour site. Sarcopenia influenced re-admissions more significantly in the gastric cancer subgroup. Additionally, sarcopenia increased the risk of total complications and infections more strongly in the colorectal cancer subgroup and affected the hospital stay more severely in the esophageal cancer subgroup. We also found that tumour site resulted in high heterogeneity in the hospital stay analysis. As a result, we should pay more attention to investigations of the specific, greater impact of sarcopenia on patients with carcinoma, such as colorectal carcinoma. Sensitivity analyses proved that our results were stable.

The main findings of this systematic review need to be considered in the context of several key limitations. First, to reduce heterogeneity from different definition criteria between studies, we included only 11 articles that defined sarcopenia using the EWGSOP or AWGS Consensus. This low number may have led to some bias in our conclusions. Secondly, we performed subgroup analysis based only on the different muscle mass measurements and tumour site due to the small number of studies. Lastly, although we suspected that the article quality might introduce some bias, due to the small number of articles with only one low-quality article included, we did not stratify another subgroup analysis.

# Conclusions

Sarcopenia defined by the EWGSOP or AWGS Consensus was associated with a high risk of adverse outcomes across digestive carcinoma patients who had received surgery. By comparing different muscle mass measurements and tumour sites, our meta-analysis suggested that more attention should be paid to comparing the best muscle mass measurement, identifying high-risk patients for sarcopenia among digestive carcinoma patients and performing more high-quality studies. Due to the lack of a universal definition of sarcopenia, the findings should be interpreted with caution.

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# **Compliance with ethical standards**

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

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