Sarcopenia does not affect postoperative complication rates in oesophageal cancer surgery: a systematic review and meta-analysis

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ABSTRACT

INTRODUCTION The high morbidity and mortality rates after oesophagectomy indicate the need for rigorous patient selection and preoperative risk assessment. Although muscle mass depletion has been proposed as a potential prognostic factor for postoperative complications and decreased survival in gastrointestinal cancer patients, available data are conflicting. The purpose of the present meta-analysis is to determine whether sarcopenia predicts postoperative outcomes in patients undergoing oesophagectomy.

METHODS The databases MEDLINE, SCOPUS, Clinicaltrials.gov, CENTRAL and Google Scholar were searched for studies reporting on the effect of sarcopenia on postoperative outcomes following oesophageal cancer surgery. Outcomes included surgical complications, anastomotic leakage, respiratory complications, cardiovascular complications, postoperative infections, major complications and overall complications. The random effects model (DerSimonian–Laird) was used to calculate pooled effect estimates when high heterogeneity was encountered, otherwise the fixed-effects (Mantel–Haenszel) model was implemented.

FINDINGS A total of eight studies involving 1488 patients diagnosed with oesophageal cancer and who underwent oesophagectomy were included in the meta-analysis. The presence of sarcopenia did not significantly increase the rate of surgical complications (odds ratio, OR, 0.86, 95% confidence interval, CI, 0.40–1.85), anastomotic leakage (OR 0.75, 95% CI 0.42–1.35), respiratory complications (OR 0.56, 95% CI 0.21–1.48), cardiovascular complications (OR 0.94, 95% CI 0.31–2.83), postoperative infection (OR 1.14, 95% CI 0.52–2.50), major complications (OR 0.81, 95% CI 0.23–2.82) or overall postoperative complications (OR 0.80, 95% CI 0.32–1.99).

CONCLUSION Sarcopenia does not seem to affect postoperative complication rates of patients undergoing oesophagectomy for oesophageal cancer. Future research should focus on determining whether prognosis differs according to muscle mass in this patient population.

KEYWORDS

Sarcopenia – Oesophageal cancer – Postoperative complications – Meta-analysis

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Introduction

Oesophageal cancer is an aggressive group of malignancies accounting for over 400,000 deaths per year.¹ Oesophagectomy, the procedure of choice in localised and regional disease, is one of the most invasive and morbid operations among gastrointestinal surgical procedures.

Patients undergoing oesophagectomy have an increased risk of postoperative complications and high mortality rates, indicating the need for rigorous patient selection and preoperative risk assessment.² Various methods of risk assessment are clinically used including the American Society of Anesthesiologists (ASA) score,³ the Physiological

and Operative Severity Score for the Enumeration of Mortality and Morbidity (P-POSSUM) scoring system that uses physiological and operative parameters,⁴ as well as the frailty index, which combines assessment of functional impairment and/or unintentional weight loss,⁵ and is mainly applicable to geriatric patients.⁶

In this context, sarcopenia is emerging as a potential prognostic factor for postoperative complications and decreased survival in gastrointestinal cancer patients, since it reflects muscle wasting and poor nutritional status.⁷ Although several definitions of the term 'sarcopenia' exist, most of them emphasise the assessment of patient muscle mass, muscle strength and physical performance.⁸ The most commonly used methods of muscle mass quantification in cancer patients are imaging techniques, such as computed tomography (CT), which is routinely performed preoperatively for cancer staging.⁹ Bioimpedance analysis is also popular because of its cost effectiveness and simplicity.¹⁰ Although there are data suggesting that sarcopenia may be related to higher risk of complications and mortality after oesophagectomy,^{11–15} a significant number of studies have failed to confirm these results.^{14,15}

In the present meta-analysis, we sought to investigate the impact of sarcopenia on the short- and long-term outcomes of patients undergoing oncologic oesophagectomy, to guide clinical decision making and operative intervention.

Methods

Study design

The present study was designed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and AMSTAR (A Measurement Tool to Assess systematic Reviews) guidelines.^{16,17} Eligibility criteria were determined by the authors. No language or date restrictions were applied during the literature search. The studies were selected in three consecutive stages. First, the titles and abstracts of all electronic articles were screened to evaluate their eligibility. Second, the articles that were presumed to meet the criteria were retrieved as full texts. In the third stage, we selected all observational studies (both prospective and retrospective) that referred to the postoperative outcomes of sarcopenic and non-sarcopenic patients diagnosed with oesophageal cancer who underwent oesophagectomy. References of full-text articles were also screened to determine whether they were eligible for inclusion in the present meta-analysis using snowball methodology. Case reports and review articles were excluded. Two authors performed the electronic search of articles and tabulated data on duplicated prestructured forms. The data were then reviewed by all authors and all conflicts were resolved by the consensus of all authors.

Literature search and data collection

We queried the databases Medline/PubMed (1966–2017), Scopus (2004–2017), Clinicaltrials.gov (2008–2017), Cochrane Central Register of Controlled Trials CENTRAL (1999–2017)

and Google Scholar (2004–2017). The date of our last search was 3 January 2018. The search strategy included the keywords 'oesophageal', 'cancer', 'surgery', 'sarcopenia', 'muscle', 'mass', 'myopenia' in combination with Boolean operators (AND, OR, NOT). The stages of article selection are depicted in the PRISMA flow diagram (Fig 1).

Quality assessment

The methodological quality of the included studies was assessed with the Newcastle–Ottawa Scale.¹⁸ According to that scale, each study is judged on eight items, categorised into three groups: the selection of the study groups, the comparability of the groups and the ascertainment of either the exposure or outcome of interest for case-control or cohort studies, respectively. Stars awarded for each quality item serve as a quick visual assessment. Stars are awarded such that the highest quality studies are awarded up to nine stars (Fig 2).

Statistical analysis

Categorical variables were summarised using frequencies and percentages, while continuous variables were summarised as means and standard deviations (SD). Based on extracted data, odds ratio (OR) and 95% confidence intervals (CI) were calculated by means of 2×2 tables for each categorical outcome; an OR greater than one denoted an outcome more frequently present in the sarcopenic group. Moreover, weighted mean difference (WMD) with its 95% CI was calculated for each continuous outcome; WMD greater than zero corresponded to larger values in the sarcopenic group. Between-study heterogeneity was assessed through the Cochran Q statistic and by estimating I^2 . High heterogeneity was confirmed with a significance level of $P < 0.05$ and I^2 value of $\geq 50\%$. The random effects model (DerSimonian–Laird) was used to calculate pooled effect estimates when high heterogeneity was encountered. The fixed-effects (Mantel–Haenszel) model was preferred when low heterogeneity was encountered. Statistical significance was set at $P < 0.05$ for all comparisons and all P -values were two-sided. All statistical analyses were performed using Review Manager (RevMan) 5.3 software.¹⁹

Publication bias was not tested due to the gross heterogeneity of included studies, which is a significant confounder that may influence the methodological integrity of these tests.²⁰

Protocol registration

This study is registered with the Research Registry (www.researchregistry.com).

Findings

Included studies

A total of eight studies were included in the present meta-analysis (Table 1).^{15,14,21–26} Overall, 1488 patients were enrolled in eligible studies, of whom 731 were non-sarcopenic and 757 were sarcopenic. A total of 1305 men and

183 women were included in our analysis. No statistically significant differences were observed in terms of age, sex, body mass index, comorbidities and respiratory conditions (forced expiratory volume in one second, FEV1, vital capacity, VC) among patients enrolled in systematically reviewed studies (Table 2). Only two of the eight studies provided data about neoadjuvant chemoradiotherapy and there no statistically significant differences between the sarcopenic and the non-sarcopenic group.

Excluded studies

Ten studies were excluded from the present meta-analysis. Four studies presented complications of neoadjuvant chemotherapy in patients with oesophageal cancer before undergoing oesophagectomy.^{15,27–29} Three other studies

used sarcopenia as a continuous variable and did not stratify the patients into two distinct groups (sarcopenic and non-sarcopenic).^{11,12,30} Park *et al* used psoas muscle mass as an indicator of sarcopenia;³¹ Heneghan included both patients who suffered from oesophageal and gastric cancers;³² and Wagner presented postoperative complications after gastrointestinal surgery in general.⁷

Data tabulation

Data on variables of interest were tabulated in four structured forms. Table 1 presents the basic study characteristics by sarcopenia definition. Table 2 includes the main patients characteristics, such as age, sex, body mass index (BMI), respiratory condition, reflected in FEV1 and VC levels, and main comorbidities, such as diabetes mellitus,

Figure 1 The PRISMA flow chart of study selection.

chronic obstructive pulmonary disease, hypertension and coronary disease. Table 3 summarises postoperative complications following oesophagectomy for sarcopenic and non-sarcopenic cancer patients. More specifically, it demonstrates surgical complications including anastomotic leakage, chylothorax, bleeding, recurrent laryngeal nerve paralysis, conduit necrosis, anastomotic stenosis and ileus; anastomotic leakage alone; the respiratory complications that include pneumonia and respiratory failure; infections that include sepsis, surgical site infection, *Clostridium difficile* infection, intrathoracic or intrabdominal abscess and central intravenous line infection; cardiovascular complications such as myocardial infarction, atrial fibrillation and other dysrhythmias, congestive heart failure, pericarditis, peripheral thrombophlebitis and deep venous thrombosis, and overall complications. Table 3 also includes postoperative complications classified according to the Dindo–Clavien system.⁵⁵ Table 4 includes the morbidity and mortality rates of the patients.

Definitions

Sarcopenia was defined as low muscle mass using a variety of cut off points in six of eight studies.^{15,14,21–26} More specifically, sarcopenia was assessed by preoperative abdominal CT in six studies (skeletal muscle index: muscle area normalised by the square of the height), whereas in the other two studies sarcopenia was defined as a combination of low muscle mass using bioelectric impedance analysis and low muscle strength and/or low physical performance. Surgical complications include anastomotic leakage,

chylothorax, bleeding, recurrent laryngeal nerve paralysis, conduit necrosis, anastomotic stenosis and ileus. Overall postoperative complications were defined as any type of complication that could develop after oesophagectomy, including infections, cardiovascular, respiratory, and surgical complications.

Complications following oesophagectomy

High heterogeneity was encountered in all meta-analyses and therefore random effect models are reported. No difference was observed in terms of surgical complications (anastomotic insufficiency, bleeding, chylothorax, laryngeal nerve palsy) between the sarcopenic and the non-sarcopenic group of patients (OR 0.86, 95% CI 0.40–1.85; Fig 3). Similarly, the rate of anastomotic leakage after oesophagectomy was not different between patients with and without sarcopenia (OR 0.75, 95% CI 0.42–1.35; Fig 4). The respiratory complications after oesophagectomy were also similar between the two groups (OR 0.56, 95% CI 0.21–1.48; Fig 5), as were the cardiovascular complications (OR 0.94, 95% CI 0.31–2.83; Fig 6). Postoperative infection rates were not significantly different between patients with and without sarcopenia (OR 1.14, 95% CI 0.52–2.50; Fig 7). Postoperative complications grade I–II (OR 1.03, 95% CI 0.29–3.63) and grade III–IV (OR 0.81, 95% CI 0.23–2.82) according to the Dindo–Clavien system were similar between the sarcopenic and the non-sarcopenic group (Fig 8).⁵⁵ Finally, overall postoperative complications after oesophagectomy did not differ between the two groups of patients (OR 0.80, 95% CI 0.32–1.99; Fig 9).

Newcastle-Ottawa Assessment Scale									
Date; Author	Selection				Comparability	Outcome			Total
	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Outcome of interest not present at start of study		Assessment of outcome	Adequacy of duration of follow up	Adequacy of completeness follow up	
2015; Ida	★	★	★	★	★	★	★	★	8
2016; Harada	★	★	★	★	★	★	★	★	8
2016; Tamandi	★	★	★	★	★	★	★		7
2016; Grotenhuis	★	★	★	★	★	★	★	★	8
2016; Makiura	★	★	★	★	★	★	★		7
2016; Nishigori	★	★	★	★	★	★	★	★	8
2016; Poireder	★	★	★	★	★	★	★	★	8
2017; Nakashima	★	★	★	★	★★	★	★		8

Figure 2 The methodological assessment of the included studies according to the Newcastle–Ottawa Scale.

Table 1 The characteristics of the included studies.

Study	Type of study	Patients (n)	Inclusion criteria	Exclusion criteria	Sarcopenia definition
Ida <i>et al</i> (2015) ²²	Prospective	138	Oesophageal squamous cell carcinoma; oesophagectomy	N/A	Values below < 90% of standard (bioelectrical impedance)
Harada <i>et al</i> (2016) ²¹	Retrospective	256	Squamous cell carcinoma; patients underwent surgical resection (2005–2011), CT available	Patients with an interrupted CRT history; patients receiving palliative CRT; palliative care	Muscle area normalised by the square of the height (m ²); cut off: (tertile 3) < 44.5cm ² /m ² for men, < 36.5cm ² /m ² for women
Tamandl <i>et al</i> (2016) ¹³	Retrospective	200	Oesophageal/gastro-oesophageal cancer; potentially curative surgery; suitability for analysis of sarcopenia and body composition parameters	Metastatic or no resection; CT images not retrievable/not complete; abdominal examination covering lumbar vertebra 3; no malignancy upon histology	SMI (cm ² /m ²) = TMA at L3/(height [m] x height [m]). Sarcopenia was defined: SMI of ≤ 39cm ² /m ² for women and ≤ 55cm ² /m ² for men
Grotenhuis <i>et al</i> (2016) ¹⁴	Retrospective	120	Oesophagectomy for cancer after neoadjuvant chemoradiotherapy; patients with a CT performed not less than 3 months before initial diagnosis of oesophageal cancer, before start of nCRT	N/A	Total cross-sectional muscle tissue measured transversely at the third lumbar level < 52.4cm ² /m ² body surface area for men, < 38.5cm ² /m ² body surface area for women (SMI-CT)
Makiura <i>et al</i> (2016) ²³	Retrospective	104	Patients with oesophageal cancer scheduled to undergo definitive oesophagectomy (2011–2015); preoperative assessment	Recurrent cancer; declined to consent	Low muscle mass and strength and/or low physical performance. Low muscle mass was defined by appendicular SMM ÷ squared height of < 7.0kg/m ² for men and < 5.7kg/m ² for women (bioelectrical impedance). Low muscle strength was defined by handgrip strength of < 26kg for men and < 18kg for women. Low physical performance was defined by gait speed of < 0.8metres/second
Nishigori <i>et al</i> (2016) ²⁵	Retrospective	199	Histological diagnosis of thoracic oesophageal cancer; patients underwent oesophagectomy followed by primary reconstruction (2005–2014)	Preoperative CT not available; preoperative chemoradiotherapy; multiple primary cancers	SMM at L3 level was normalised to patient's height to calculate SMI-CT (cm ² /m ²). Cut-off sarcopenia: 52.4cm ² /m ² for men and 38.5cm ² /m ² for women
Paireder <i>et al</i> (2016) ²⁶	Retrospective	130	Consecutive patients who underwent oesophageal resection for oesophageal cancer (2006–2013); neoadjuvant treatment	Missing pre- or post-therapeutic CT	SMI-CT calculated as TMA/height (m) x height (m). Sarcopenia defined as a reduced SMI of ≤ 39cm ² /m ² for women and ≤ 55cm ² /m ² for men
Nakashima <i>et al</i> (2018) ²⁴	Retrospective	341	Consecutive patients who underwent oesophagectomy for oesophageal cancer (2004–2014)	Data not available from preoperative CT	Oesophageal cancer-specific assessment for sarcopenia, median SMI as cut-off values by sex: 47.24cm ² /m ² in men and 36.92cm ² /m ² in women SMI (cm ² /m ²) CT

CT, computed tomography; N/A, not available; nCRT, neo-adjuvant chemoradiotherapy; SMI, skeletal muscle index; SMM, skeletal muscle mass; TMA, total muscle area.

Table 2 Characteristics of the patients in the included studies.						
Study	Age (years $\pm$ SD)	Sex (n)	Body mass index (kg/m ²)	Comorbidities (n) ^a	FEV 1 (n)	VC (n)
Ida <i>et al</i> (2015) ²²	63.1 $\pm$ 0.9 vs 67.8 $\pm$ 1.0	female: 3 vs 14 male: 74 vs 47	23.6 $\pm$ 0.3 vs 20.4 $\pm$ 0.3	DM: 10 vs 8, COPD: 22 vs 21, CD: 42 vs 33	72.7 $\pm$ 1.1 vs 73.3 $\pm$ 1.3	106.3 $\pm$ 1.7 vs 100.3 $\pm$ 1.9
Harada <i>et al</i> (2016) ²¹	N/A	N/A	N/A	N/A	N/A	N/A
Tamandl <i>et al</i> (2016) ¹³	61.1 vs 65.6	female: 26 vs 23 male: 44 vs 107	26.9 vs 23.7	N/A	N/A	N/A
Grotenhuis <i>et al</i> (2016) ¹⁴	59 vs 64	female: 20 vs 12 male: 46 vs 42	28 vs 25	N/A	N/A	N/A
Makiura <i>et al</i> (2016) ²³	64 vs 69	female: 9 vs 7 male: 66 vs 22	21.7 $\pm$ 2.8 vs 19.3 $\pm$ 2.6	DM: 7 vs 3, HT: 34 vs 8, COPD: 20 vs 11, CD: 4 vs 5	74.1 $\pm$ 9.5 vs 70.4 $\pm$ 12.7	100.1 $\pm$ 12.0 vs 93.2 $\pm$ 14.2
Nishigori <i>et al</i> (2016) ²⁵	64.8 $\pm$ 7.8 vs 65.4 $\pm$ 7.7	female: 19 vs 16 male: 31 vs 133	22.3 $\pm$ 2.7 vs 20.5 $\pm$ 2.7	DM: 3 vs 17	77.2 $\pm$ 9.38 vs 74 $\pm$ 8.8	116.2 $\pm$ 13.5 vs 111 $\pm$ 14.8
Paireder <i>et al</i> (2016) ²⁶	61.3 vs 63.8	female: 12 vs 12 male: 38 vs 68	26.5 vs 23.7	N/A	N/A	N/A
Nakashima <i>et al</i> (2018) ²⁴	N/A	N/A	N/A	N/A	N/A	N/A

^a Chronic obstructive pulmonary disease (COPD), coronary disease (CD), diabetes mellitus (DM), hypertension (HT).
N/A, not available; FEV1, forced expiratory volume in the first second; SD, standard deviation; VC, vital capacity.

Study	Surgical^a n (%)	Anastomotic leakage n (%)	Respiratory^b n (%)	Infections^c n (%)	Cardiovascular n (%)	Overall complications n (%)	I-II	III-V
Ida <i>et al</i> (2015) ²²	12 (9) vs 8 (6)	12 (9) vs 8 (6)	9 (7) vs 21 (15)	20 (15) vs 16 (11)	6 (4) vs 5 (3)	N/A	N/A	N/A
Harada <i>et al</i> (2016) ²¹	69 (40) vs 35 (42)	24 (14) vs 21 (25)	31 (18) vs 13 (15)	52 (37) vs 31 (30)	3(2) vs 2(2)	113 (66) vs 55 (65)	52 (31) vs 21 (25)	61 (35) vs 34 (40)
Tamandl <i>et al</i> (2016) ¹³	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Grotenhuis <i>et al</i> (2016) ¹⁴	N/A	N/A	N/A	N/A	N/A	45 (68) vs 42 (78)	30 (45) vs 26 (48)	15 (23) vs 16 (30)
Makiura <i>et al</i> (2016) ²³	9 (12) vs 6 (21)	N/A	13 (17) vs 11 (38)	10 (13) vs 5 (17)	17 (22) vs 9 (31)	N/A	N/A	N/A
Nishigori <i>et al</i> (2016) ²⁵	8 (16) vs 33 (22)	4 (8) vs 20 (13)	6 (8) vs 52 (13)	10 (20) vs 26 (17)	4 (8) vs 17 (11)	24 (48) vs 79 (53)	15 (30) vs 41 (28)	13 (26) vs 41 (27)
Paireder <i>et al</i> (2016) ²⁶	8 (16) vs 14 (18)	8 (16) vs 9 (11)	4 (8) vs 11 (14)	N/A	N/A	10 (20) vs 18 (23)	N/A	N/A
Nakashima <i>et al</i> (2018) ²⁴	28 (16) vs 42 (28)	28 (16) vs 42 (28)	13 (8) vs 18 (11)	N/A	N/A	53 (31) vs 59 (38)	N/A	N/A

^aAnastomotic insufficiency, bleeding, chylothorax etc.
^bPneumonia, failure etc.
^cSurgical site, sepsis etc.
N/A, not available.

Table 4 Healthcare metrics of the included studies.									
Study	Hospital stay (days $\pm$ SD)	In-hospital mortality (n)	Mortality (n)	Operation time (minutes $\pm$ SD)	Blood loss (ml $\pm$ SD)	Survival (months)	Relapse-free survival (months)		
Ida <i>et al</i> (2015) ²²	28.1 $\pm$ 2.1 vs 33.7 $\pm$ 2.4 (<i>P</i> = 0.11)	0 vs 0 (<i>P</i> = 0.36)	N/A	612.9 $\pm$ 12.9 vs 557.4 $\pm$ 14.5 (<i>P</i> = 0.01)	687.5 $\pm$ 176.2 vs 781.5 $\pm$ 198.0 (<i>P</i> = 1.00)	N/A	N/A		
Harada <i>et al</i> (2016) ²¹	N/A	0	N/A	535 $\pm$ 11.6 vs 559 $\pm$ 16.5 (<i>P</i> = 0.25)	587 $\pm$ 35.0 vs 609 $\pm$ 50.0 (<i>P</i> = 0.71)	N/A	N/A		
Tamandl <i>et al</i> (2016) ¹³	N/A	N/A	N/A	N/A	N/A	76.5 vs 31.5 (<i>P</i> = 0.011)	N/A		
Grotenhuis <i>et al</i> (2016) ¹⁴	14 vs 14 (<i>P</i> = 0.65)	3 vs 3 (<i>P</i> = 0.8)	N/A	396 vs 420 (<i>P</i> = 0.3)	N/A	32 vs 22 (BMI $\leq$ 25) 28 vs 25 (BMI > 25) (<i>P</i> = 0.77)	29 vs 22 (BMI $\leq$ 25) 26 vs 23 (BMI > 25) (<i>P</i> = 0.35)		
Makiura <i>et al</i> (2016) ²³	28 vs 53 (<i>P</i> < 0.001)	N/A	N/A	715 vs 711 (<i>P</i> = 0.5)	5.6 vs 10.9 (<i>P</i> < 0.001)	N/A	N/A		
Nishigori <i>et al</i> (2016) ²⁵	N/A	1 vs 1	N/A	N/A	N/A	N/A	Not reached vs 15.8 (<i>P</i> = 0.068)		
Paireder <i>et al</i> (2016) ²⁶	N/A	N/A	N/A	N/A	N/A	52.1 vs 20.5 (<i>P</i> = 0.036)	N/A		
Nakashima <i>et al</i> (2018) ²⁴	N/A	3 vs 5	1 vs 0	N/A	N/A	< 65 years: 55.6% vs 44.9% (5-year) (<i>P</i> = 0.1136) $\geq$ 65: 56% vs 26.5% (5-year) (<i>P</i> < 0.0001)	N/A		

Survival after oesophagectomy

Four studies reported on prognosis after surgery. The patients without sarcopenia had higher survival rates after oesophagectomy compared with the sarcopenic group in most studies.^{15,14,24,26} In addition, Tamandl *et al* presented longer survival interval for patients without sarcopenia compared with those with sarcopenia (76.5 vs 31.5 months, $P = 0.011$),¹⁵ as did Paireder *et al* (52.1 vs 20.5 months, $P = 0.036$).²⁶ Nakashima *et al* highlighted a higher five-year survival rate for patients without sarcopenia who were over 65 years of age compared with those with sarcopenia above 65 years old (56% vs 26.5%, $P < 0.0001$).²⁴

Healthcare metrics

The included studies provided only few data with missing standard deviations of some healthcare metrics after oesophagectomy, which led to the preclusion of these parameters from a meta-analysis. Ida *et al* presented a shorter hospital stay for patients without sarcopenia (28.1 ± 2.1 vs 33.7 ± 2.4 days), although it was not statistically significant

($P = 0.11$), no difference in in-hospital mortality (0 vs 0, $P = 0.36$), a longer operation time for patients without sarcopenia compared with the sarcopenic group (612.9 ± 12.9 vs 557.4 ± 14.5 minutes, $P = 0.01$) and similar blood loss (687.5 ± 176.2 vs 781.5 vs 198.0 ml, $P = 1.00$).²²

Makiura *et al* demonstrated a shorter hospital stay for patients without sarcopenia compared with the sarcopenic group (28 vs 53 days, $P < 0.001$), similar operation time between the two groups (715 minutes vs 711 minutes, $P = 0.5$) and greater blood loss (5.6ml/kg vs 10.9ml/kg, $P < 0.001$) for the sarcopenic group.²³ Harada *et al* reported similar operation time (535 minutes $\pm$ 11.6 minutes vs 559 minutes $\pm$ 16.5 minutes, $P = 0.25$) and blood loss (587ml $\pm$ 35.0ml vs 609ml $\pm$ 50.0ml, $P = 0.71$) between the two groups.²¹ Tamandl *et al* showed a greater survival for non-sarcopenic patients (76.5 months vs 31.5 months, $P = 0.011$).¹⁵ Moreover, Grotenhuis *et al* presented similar hospital stay (14 days vs 14 days, $P = 0.65$), similar in-hospital mortality (three deaths in each group, $P = 0.8$), similar operation time (396 minutes vs 420 minutes, $P = 0.3$),

Figure 3 Odds ratio according to surgical complications (anastomotic insufficiency, bleeding, chylothorax etc.). The overall effect was not statistically significant ($P > 0.05$). Vertical line: no difference point between two groups; squares: odds ratios; Diamonds: pooled odds ratio for all studies; horizontal lines, 95% confidence intervals (CI).

Figure 4 Odds ratio according to anastomotic leakage. The overall effect was not statistically significant ($P > 0.05$). Vertical line, no difference point between two groups; squares, odds ratios; diamonds, pooled odds ratio for all studies; horizontal lines, 95% confidence intervals (CI).

similar survival (32 months vs 22 months for those with a BMI < 25kg/m² and 28 months vs 25 months for those with BMI > 25, $P = 0.77$) and similar relapse free survival between the two groups (29 months vs 22 months for those with BMI < 25 and 26 months vs 23 months for those with BMI > 25, $P = 0.35$).¹⁴ Nishigori *et al* demonstrated no difference between the two groups of patients in terms of in-hospital mortality (one death in each group, P -value not available) and relapse free survival (not reached vs 15.8 months, $P = 0.068$).²⁵ Paireder *et al* reported a lower survival for the patients with sarcopenia (52.1 months vs 20.5 months, $P = 0.036$).²⁶ Finally, Nakashima *et al* showed a similar in-hospital mortality (3 deaths vs 5 deaths, P -value not available), a similar mortality (1 death vs 0 deaths, P -value not available) and a similar five-year survival rate between the two groups for patients younger than 65 years (55.6% vs 44.9%, $P = 0.1136$). However, the five-year survival rate was higher in patients without sarcopenia who were older than 65 years (56% vs 26.5%, $P < 0.0001$).²⁴

Quality assessment

The Newcastle–Ottawa scale was used for quality assessment.¹⁸ Four studies were awarded six stars, one was awarded four stars and the remaining 13 studies were awarded five stars (Fig 2).

Discussion

Oesophageal malignancies are typically associated with high mortality rates and substantial morbidity following oesophagectomy. Although several predictors of outcome have been identified (eg stage, surgical technique),^{34,35} the role of sarcopenia in determining prognosis remains unclear. The present meta-analysis investigated the potential impact of sarcopenia on postoperative outcomes after oesophagectomy for patients with oesophageal cancer. Pre-operative sarcopenia did not seem to be associated with overall complications or with the surgical complications in total. Particularly, anastomotic leakage, respiratory complications, cardiovascular complications and postoperative

infections after oesophagectomy did not seem to be affected by the preoperative nutritional state of patients. On the other hand, certain studies suggest that non-sarcomenic status before surgery may be related with shorter length of hospital stay, longer disease-free survival and higher five-year survival rate for patients older than 65 years.^{15,14,24,26}

Our findings are in accordance with prior studies that examined the effect of sarcopenia on postoperative outcomes of patients undergoing surgery due to other types of gastrointestinal malignancies. For instance, the rate of

surgical complications did not differ between patients with and without sarcopenia who were treated for gastric cancer with radical gastrectomy.⁵⁶ Sheetz *et al* indicated that a lean psoas area, representing diminished core muscle size, was not associated with anastomotic leakage in 250 patients subjected to oesophagectomy.¹² Van Dijk *et al* demonstrated that sarcopenia, estimated from preoperative CT scans, was not predictive of anastomotic leakage in a prospective cohort of 199 patients with pancreatic cancer.⁵⁷ Similarly, sarcopenia does not seem to affect the anastomotic leakage rate in colorectal cancer surgery.⁵⁸

Figure 7 Odds ratio according to infection rates. The overall effect was not statistically significant ($P > 0.05$). Vertical line, no difference point between two groups; squares, odds ratios; diamonds, pooled odds ratio for all studies; horizontal lines, 95% confidence intervals (CI).

Figure 8 Odds ratio according to the Clavien–Dindo classification of complications. The overall effect was not statistically significant ($P > 0.05$). Vertical line, no difference point between two groups; squares, odds ratios; diamonds, pooled odds ratio for all studies; horizontal lines, 95% confidence intervals (CI).

Therefore, current evidence suggests that postoperative surgical complications and major anastomotic leaks might be influenced by other factors, such as the presence of comorbidities,⁵⁹ obesity and the type of surgical procedure and anastomosis.⁴⁰

Our meta-analysis corroborates and expands upon the results of recent evidence-based medicine research suggesting no increased risk of non-pulmonary postoperative complications in patients with sarcopenia (including anastomotic leak, cardiac complications and surgical site infections). Not surprisingly, published studies seem to associate superior preoperative nutrition status with improved overall survival.^{15,14,24,26} Boshier *et al* meta-analysed survival data in an attempt to provide pooled statistical evidence of sarcopenia's influence on prognosis and demonstrated that sarcopenia was associated with lower overall survival. Given that the majority of the available studies did not provide measures of statistical dispersion the authors used 'annual mortality rates, survival curves, number of deaths or percentage freedom from death' to approximate pooled summary statistics for survival.⁴¹ These and various other forms of imputation have been described to deal with missing data in the setting of a meta-analysis. Several methodological concerns surround these techniques including the potential to introduce substantial bias to the analysis.^{42,43} Indeed, Boshier *et al* reported high heterogeneity (I², 61.7%) in the long-term survival outcome. Considering the aforementioned limitations, we opted to qualitatively assess survival data. This approach may be safer and potentially more appropriate from a methodological standpoint.

To our knowledge, this is the first systematic literature review investigating the impact of sarcopenia on oesophagectomy outcomes for patients with oesophageal cancer. The methodological strengths of the present paper include protocol registration to an international database, a comprehensive literature search following a rigorous and systematic methodology, detailed data extraction with pre-piloted forms, and standardised quality assessment of

eligible studies using the well-validated modified Newcastle–Ottawa scale.

This analysis has certain limitations. As with any systematic review, certain studies did not report on all outcomes of interest and all statistical analyses were performed using available data. Most importantly, although certain studies presented data on postoperative survival,^{15,14,24,26} no standard deviations were provided, so it was impossible to run a meta-analysis with prognosis as the outcome of interest. Furthermore, our analysis only includes studies that defined sarcopenia as a dichotomous variable (not as a continuous parameter), despite the fact that the assessment of sarcopenia was not the same for all studies.

The retrospective nature of the majority of the included studies constitutes another important limitation of our study. Additionally, the wide variety of cut-off points and methods that were used for the assessment of sarcopenia resulted in different definitions of sarcopenia and high heterogeneity among studies. Finally, the addition of new therapeutic strategies, such as neoadjuvant chemotherapy in recent years has influenced the assessment and comparison of postoperative outcomes between studies that present a quite large difference on the time that surgery took place. For that reason, future studies should include neoadjuvant chemoradiotherapy as a strong confounding factor in their comparisons in the terms of survival and morbidity after oesophagectomy.

Conclusions

Contrary to the widespread belief of the surgical community, our study demonstrates that sarcopenia does not seem to affect the postoperative complication rates of patients undergoing oesophagectomy for oesophageal cancer. For that reason, the nutritional status of patients suffering from oesophageal cancer should not remain a contraindication for surgical excision. Consequently, surgeons should consider both the low impact of sarcopenia in postoperative

complications and the serious impact on survival rates and choose the best therapeutic strategy according to other parameters for each patient. Future research should focus on determining whether prognosis differs according to muscle mass in this patient population.

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