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## Review

# Prognostic value of sarcopenia in adults with solid tumours: A meta-analysis and systematic review



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## KEYWORDS

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Prognostic factor;  
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Cancer

**Abstract** **Background:** Body composition plays an important role in predicting treatment outcomes in adults with cancer. Using existing computed tomographic (CT) cross-sectional imaging and readily available software, the assessment of skeletal muscle mass to evaluate sarcopenia has become simplified. We performed a systematic review and meta-analysis to quantify the prognostic value of skeletal muscle index (SMI) obtained from cross-sectional CT imaging on clinical outcomes in non-haematologic solid tumours.

**Methods:** We searched PubMed and the American Society Clinical Oncology online database of meeting abstracts up to October 2015 for relevant studies. We included studies assessing the prognostic impact of pre-treatment SMI on clinical outcomes in patients with non-haematologic solid tumours. The primary outcome was overall survival (OS) and the secondary outcomes included cancer-specific survival (CSS), disease-free survival (DFS), and progression-free survival (PFS). The summary hazard ratio (HR) and 95% confidence interval (CI) were calculated.

**Results:** A total of 7843 patients from 38 studies were included. SMI lower than the cut-off was associated with poor OS (HR = 1.44, 95% CI = 1.32–1.56,  $p < 0.001$ ). The effect of SMI on OS was observed among various tumour types and across disease stages. Worse CSS was also associated with low SMI (HR = 1.93, 95% CI = 1.38–2.70,  $p < 0.001$ ) as well as DFS (HR = 1.16, 95% CI = 1.00–1.30,  $p = 0.014$ ), but not PFS (HR = 1.54, 95% CI = 0.90–2.64,  $p = 0.117$ ).

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**Conclusions:** This meta-analysis demonstrates that low SMI at cancer diagnosis is associated with worse survival in patients with solid tumours. Further research into understanding and mitigating the negative effects of sarcopenia in adults with cancer is needed.  
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## 1. Introduction

Great heterogeneity exists in the ability of adults with cancer to tolerate treatment. Although major advances have been made in cancer research, it remains difficult to predict which patients are at increased risk for toxicity and short survival. No clinical factors routinely collected during the cancer diagnosis evaluation, such as age, performance status, and comorbidities, are able to reliably predict toxicity or survival.

The term sarcopenia was first used by Baumgartner to describe the age-related loss of muscle mass seen in older adults. He described an index of relative muscle mass (using dual-energy X-ray absorptiometry [DEXA]) calculated as the appendicular skeletal muscle mass divided by the square of height ( $m^2$ ). Sarcopenia, defined as muscle mass two standard deviations below the mean muscle mass of healthy younger adults, was shown to be prevalent in adults with cancer and common chronic comorbidities such as heart failure and chronic obstructive pulmonary disease [1,2].

Over the last decade, the definition of sarcopenia has been adapted in oncology as severe muscle loss and has been associated with adverse outcomes. A high prevalence of sarcopenia in adults with cancer has been described; for example, 57% of patients with gastric cancer, 27.5% of patients with advanced hepatocellular carcinoma (HCC), and 29% of patients with metastatic renal cell carcinoma [3–5]. The presence of sarcopenia in adults with cancer has been associated with increased chemotherapy toxicity, post-operative complications, and poorer overall survival (OS) [6]. Although quantification of skeletal muscle is not yet a standard

component of the assessment of newly diagnosed adults with cancer, computed tomographic (CT) images, frequently obtained as part of cancer staging and metastatic disease assessment, can be used to assess skeletal muscle mass and provide prognostic information in cancer populations.

Consistent methods for CT defined cross-sectional image analysis using the third lumbar vertebra (L3) as a standard bony landmark have been defined. At this vertebral level, the cross-sectional areas are linearly related to whole-body muscle mass ( $r^2 = 0.86$ ) [6] (example given in Fig. 1). The purpose of this meta-analysis is to summarise the published findings on CT-defined skeletal muscle at L3 in adults with cancer and better understand its relationship with cancer outcomes.

## 2. Methods

### 2.1. Data source

This analysis was performed in accordance with the preferred reporting items for systematic reviews and meta-analyses statement [7]. We conducted an independent review of PubMed from January 1966 to July 2015. Search terms included ‘sarcopenia’, ‘cancer’, or ‘carcinoma’. We searched abstracts from the American Society of Clinical Oncology conferences held up to October 2015 and virtual meeting presentations utilising the same search terms to identify relevant studies. An independent search of the web of science, Embase, and Cochrane electronic databases was also performed to ensure that no additional studies were overlooked. In

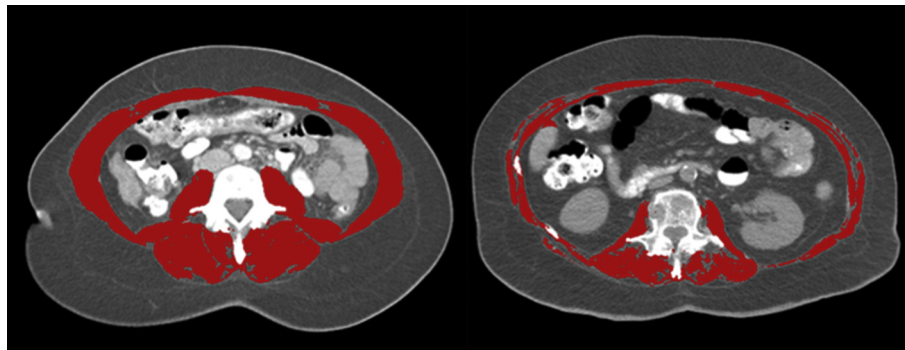


Fig. 1. Normal versus sarcopenic cancer patients. Left image: normal and right image: sarcopenic. For both metastatic cancer females, body mass index = 26.

cases of duplicate publications, only the most complete, recent, and updated report of the study was included.

## 2.2. Study selection

Studies that met the following criteria were included: (1) studies of patients with non-haematologic solid tumours; (2) assessment of the prognostic impact of pre-treatment sarcopenia measured by skeletal mass index (SMI) at L3 level on OS, cancer-specific survival (CSS), disease-free survival (DFS), recurrence-free survival (RFS) and/or progression-free survival (PFS); (3) reporting a hazard ratio (HR) and 95% confidence interval (CI) or Kaplan–Meier survival curves from which an HR could be calculated; and (4) reporting a dichotomous cut-off value for SMI. Exclusion criteria were as follows: (1) studies of patients with haematologic malignancies; (2) reporting insufficient data for estimating an HR and 95% CI; (3) reporting sarcopenia measured in different methods than SMI, and (4) reporting sarcopenia only as a continuous variable. Independent reviewers (S.S.S and T.F.N) screened reports that included the key terms in their titles and abstracts for relevance after which full texts of the relevant articles were retrieved to assess eligibility. The references from relevant reports were also reviewed manually.

## 2.3. Data extraction

Two investigators (S.S.S and T.F.N) independently performed data extraction. The following information was recorded for each study: first author's name, year of publication, disease site, disease stage (non-metastatic, metastatic/advanced, and mixed [non-metastatic and metastatic]), number of patients included in the analysis, median age, follow-up duration, cut-off defining low SMI for males and females, percentage of sarcopenic patients, and HRs with associated 95% CIs or *p* value for OS, CCS, DFS, RFS or PFS (Table 1). HRs were extracted from multivariable analyses where available. Otherwise, HRs from univariable analyses were extracted or estimated from Kaplan–Meier survival curves [8]. Any discrepancies between reviewers were resolved by consensus.

## 2.4. Statistical analysis

The primary objective of this study was to assess the association of sarcopenia with OS in patients with solid tumours. CSS, DFS (or RFS), and PFS were secondary outcomes. The summary measures of OS, CSS, DFS and PFS were HRs and corresponding 95% CIs which were extracted from each study. When those data were not reported in the publications, we calculated the HR estimates and their 95% CIs in each study using the abstracted survival probabilities in the Kaplan–Meier curve at specific time points according to the methods

proposed by Parmar et al. [8]. Statistical heterogeneity in the results between studies included in the meta-analysis was examined using Cochrane's *Q* statistic, and inconsistency was quantified with  $I^2$  statistic ( $100\% \times [Q - df]/Q$ ) that estimates the percentage of total variation across studies due to heterogeneity rather than chance [9]. The assumption of homogeneity was considered invalid for *p* values less than 0.10. Summary HRs were calculated using random-effects or fixed-effects models depending on the heterogeneity of included studies. When substantial heterogeneity was not observed, the pooled estimate calculated based on the fixed-effects model was reported by using inverse variance method. When substantial heterogeneity was observed, the pooled estimate calculated based on the random-effects model was reported by using the DerSimonian and Laird method, which considers both within-study and between-study variations [10]. Pre-specified exploratory subgroup analyses were performed according to tumour type, disease stage, and SMI cut-off value. Differences in the HRs between the subgroups were assessed using *Q* statistics. We evaluated publication bias using funnel plots and with the Begg and Egger tests [11,12]. A two-tailed *p* value of less than 0.05 was considered statistically significant. Statistical analyses were performed by using the comprehensive meta-analysis program (Version 2, Biostat, Englewood, NJ, USA).

## 3. Results

### 3.1. Search results and population characteristics

Our search strategy yielded 391 potentially relevant publications. We excluded 2 studies which reported SMI only as a continuous variable and 14 studies which reported the prognostic impact of SMI measured by psoas measurement only. Six studies that reported haematological malignancies were excluded. Ultimately, 298 citations were excluded. We included an additional publication identified through manual review of references [13]. This selection process and reasons for study exclusion are shown in Flow diagram (Fig. 2). A final total of 38 studies with 7843 patients were considered eligible for the meta-analysis (see characteristics in Table 1). Most of these studies have been published since 2012. The most common underlying malignancy included was HCC (11 studies) [5,14–23]. Other common malignancies included pancreaticobiliary cancer (*n* = 6) [24–29], gastroesophageal (*n* = 4) [30–33], urothelial cancer (*n* = 4) [34–37], renal cell carcinoma (*n* = 3) [4,38,39], colorectal (*n* = 3) [40–42] and other malignancies or mixed studies (*n* = 7) [13,43–48]. Most studies used the same established cut-offs for defining sarcopenia [13,45]. The baseline characteristics in each study are presented in Table 1. For the primary outcome of this study (HR for OS), the Begg tests showed no evidence of bias (*p* = 0.31). However, the funnel plot

Table 1  
Characteristics of the studies included in the meta-analysis.

Author (year)	Cancer	Stage	No. of patients	Age <sup>a</sup>	FU (months)	Cut point, female <sup>b</sup>	Cut point, male <sup>b</sup>	Sarcopenia (%)
Choi (2015) [24]	Pancreatic cancer	Metastatic/advanced	484	60 (20–85)	11 (10–12)	33.9	42.2	21
Cooper (2015) [25]	Pancreatic cancer	Non-metastatic	89	63 (38–79)	NR	38.9	55.4	52
Dalal (2012) [26]	Pancreatic cancer	Metastatic/advanced	41	59 (42–81)	NR	38.5	52.4	63
Dhooge (2012) [14]	HCC	Metastatic/advanced	32	NR	NR	38.9	55.4	51
Fujiwara (2015) [15]	HCC	Mixed	1257	68.8	NR	29.6	36.2	11
Fukushima (2015) [38]	Renal cell carcinoma	Metastatic/advanced	92	65 (37–91)	19 (1–142)	41	43/53 <sup>c</sup>	68
Fukushima (2015) [34]	Urothelial carcinoma	Metastatic/advanced	88	68 (39–91)	13 (1–99)	41	43/53 <sup>c</sup>	60
Harada (2015) [30]	Oesophageal cancer	Non-metastatic	325	NR	50	36.5	44.5	33
Harimoto (2013) [16]	HCC	Non-metastatic	186	NR	NR	41.1	43.75	40
Iritani (2015) [17]	HCC	Mixed	217	72 (27–90)	21 (1–74)	29	36	11
Itoh (2014) [18]	HCC	Non-metastatic	190	NR	NR	41.1	43.75	NR
Kamachi (2015) [19]	HCC	Non-metastatic	92	72 (47–84)	30 (4–108)	38.5	52.4	66
Levolger (2015) [20]	HCC	Non-metastatic	90	NR	22.5 (0–120)	39.5	52	58
Martin (2013) [13]	RT and GI cancers	Mixed	1473	NR	21 (17–25)	41	43/53 <sup>c</sup>	NR
Meza-Junco (2013) [21]	HCC	Non-metastatic	116	58 (40–84)	12 (1–66)	41	43/53 <sup>c</sup>	30
Mir (2012) [27]	Biliary cancer	Metastatic/advanced	28	63 (41–83)	6 (1–20)	38.9	55.4	36
Mir (2012) [5]	HCC	Metastatic/advanced	40	63 (32–79)	NR	38.9	55.4	28
Mir (2012) [22]	HCC	Metastatic/advanced	18	64 (25–77)	4 (1–16)	38.9	55.4	50
Miyamoto (2015) [40]	Colorectal cancer	Non-metastatic	220	70 (30–93)	43 (1–101)	42.1	49.5	25
Parsons (2012) [44]	Mixed phase I	Metastatic/advanced	104	NR	NR	38.5	52.4	51
Parsons (2012) [43]	Mixed	Metastatic/advanced	48	56 (32–76)	NR	38.5	52.4	42
Prado (2008) [45]	RT and GI cancers	Mixed	250	64 (35–88)	NR	38.5	52.4	15
Psutka (2014) [36]	Urothelial carcinoma	Non-metastatic	205	71 (63–78)	80 (71–122)	39	55	69
Psutka (2015) [39]	Renal cell carcinoma	Non-metastatic	387	65 (55–73)	86 (60–116)	39	55	47
Psutka (2015) [35]	Urothelial carcinoma	Non-metastatic	262	NR	76 (68–114)	39	55	68
Rodrigues (2013) [46]	Mixed phase I	Metastatic/advanced	306	56 (16–84)	NR	38.5	52.4	47
Rollins (2015) [28]	Pancreaticobiliary cancer	Metastatic/advanced	151	NR	NR	41	43/53 <sup>c</sup>	61
Sharma (2014) [47]	Penile cancer	Non-metastatic	43	66 (51–74)	12 (5–31)	NR	55	51
Sharma (2015) [4]	Renal cell carcinoma	Metastatic/advanced	93	61 (56–68)	13 (5–31)	41	43/53 <sup>c</sup>	29
Stene (2015) [48]	NSCLC	Metastatic/advanced	35	67 (56–86)	NR	38	52.4	74
Taguchi (2015) [37]	Urothelial carcinoma	Metastatic/advanced	64	68 (63–73)	NR	39	55	NR
Tamandl (2015) [31]	Oesophageal or GEJ cancer	Non-metastatic	200	64 (57–70)	35 (28–42)	39	55	65
Tan (2009) [29]	Pancreatic cancer	Metastatic/advanced	111	64.4	NR	38.5	52.4	56
Tan (2015) [32]	Oesophagus-gastric cancer	Non-metastatic	89	65.8	NR	38	52.4	49
Thoresen (2013) [41]	Colorectal cancer	Metastatic/advanced	77	63 (22–85)	NR	38.5	52.5	39
Van Vledder (2012) [42]	Colorectal cancer	Metastatic/advanced	196	65 (31–86)	30 (1–97)	41.1	43.75	19

(continued on next page)

Table 1 (continued)

Author (year)	Cancer	Stage	No. of patients	Age <sup>a</sup>	FU (months)	Cut point, female <sup>b</sup>	Cut point, male <sup>b</sup>	Sarcopenia (%)
Voron (2015) [23]	HCC	Non-metastatic	109	61.6	21 (14–29)	38.9	52.4	54
Yip (2013) [33]	Oesophageal cancer	Non-metastatic	35	63 (34–78)	24	38.5	52.4	26

Abbreviations: FU, follow-up; HCC, hepatocellular carcinoma; RT, respiratory tract; GI, gastrointestinal; NSCLC, non-small cell lung cancer; GEJ, gastroesophageal junction; NR, not reported.

<sup>a</sup> Mean or median as published.

<sup>b</sup> cm<sup>2</sup>/m<sup>2</sup>.

<sup>c</sup> Different cut point for body mass index <25/cut point and for body mass index >25 was utilised.

and Egger test suggested evidence of publication bias ( $p < 0.001$ ).

### 3.2. Primary outcome

A total of 7779 patients from 37 studies were included in the analysis of HRs for OS. In comparison with a high SMI, a low SMI was significantly associated with poorer OS (HR = 1.437, 95% CI = 1.321–1.563,  $p < 0.001$ , Fig. 3). The test for heterogeneity was significant and a random-effects model was used ( $Q = 224.91$ ,  $p < 0.001$ ,  $I^2 = 83.99$ ). Exploratory subgroup analysis according to the type of tumour showed the negative prognostic effect of a low SMI among most tumour types (see Table 2). In the subgroup analysis by disease stage, a prognostic role of SMI was observed for metastatic/

advanced disease (HR = 1.37, 95% CI = 1.21–1.56,  $p < 0.001$ ), non-metastatic disease (HR = 1.54, 95% CI = 1.32–1.805,  $p < 0.001$ ), and a mixed group including both metastatic and non-metastatic diseases (HR = 2.05, 95% CI = 1.27–3.28,  $p < 0.001$ ). Although the prognostic effect of SMI was numerically higher in the non-metastatic disease group, there was no statistically significant difference between the disease stages ( $p$  for subgroup difference = 0.193). HRs were extracted from multivariable analyses in 22 studies and from univariable analysis in 15 studies. An HR and its 95% CI were estimated from Kaplan–Meier survival curve in ten studies [5,14,17,22,27,30,32,33,43,47]. A separate analysis using only the studies reporting HRs for OS by multivariate analyses demonstrated a summary HR of 1.513 (95% CI = 1.35–1.69,  $p < 0.001$ ); we

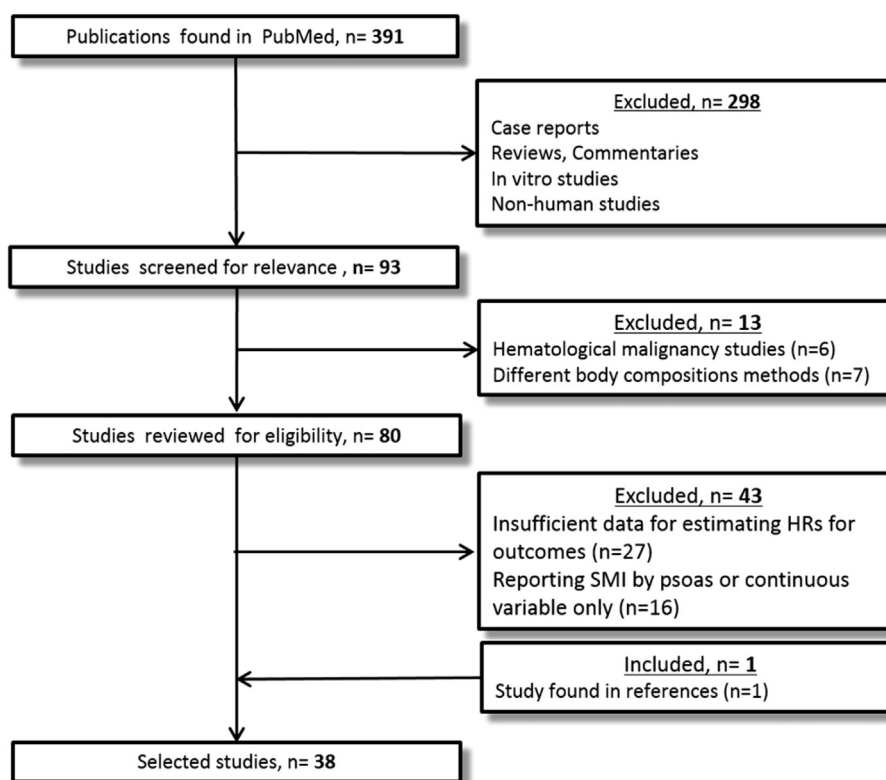
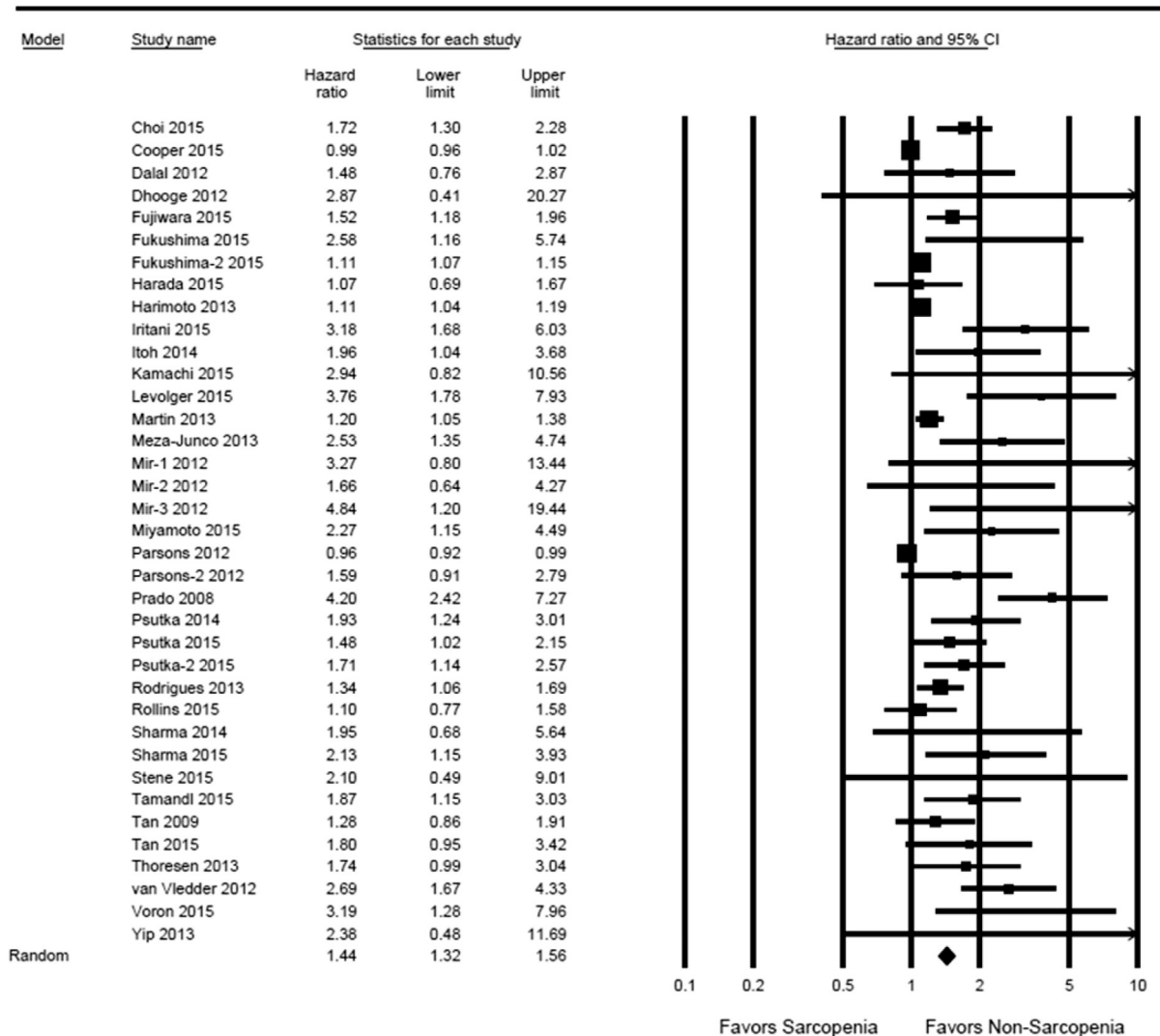


Fig. 2. Flow diagram: selection process for the studies. Abbreviation: SMI, skeletal mass index; HR, Hazard ratios.





#### Hazard ratios for OS

Fig. 3. Forest plots of hazard ratios for OS. Abbreviation: OS, overall survival.

also performed a separate analysis only using studies reporting HRs by the univariate analyses and demonstrated a summary HR of 1.556 (95% CI = 1.24–1.95,  $p < 0.001$ ) that was similar to the result of the multivariate analysis.

#### 3.3. Secondary outcomes

A total of three studies comprising 656 patients were available for the analysis of HRs for CSS. A low SMI was associated with worse CSS (HR = 1.93, 95% CI = 1.38–2.70,  $p < 0.001$ , Fig. 4). The fixed-effects model was used for the HR analysis because there was a significant heterogeneity ( $Q = 0.40$ ,  $p = 0.81$ ,  $I^2 < 0.001$ ). A meta-analysis of HRs for DFS (or relapse-free survival) was performed on 7 studies comprising 1377 patients, and the negative prognostic

effect of a low SMI on DFS was again seen (HR = 1.16, 95% CI = 1.03–1.30,  $p = 0.014$ , Fig. 4) using the random-effects model (heterogeneity test:  $Q = 29.67$ ,  $p < 0.001$ ,  $I^2 = 79.78$ ). A meta-analysis of HRs for PFS was performed on 4 studies comprising 118 patients. A negative prognostic effect of a low SMI on PFS was not observed (HR = 1.54, 95% CI = 0.90–2.64,  $p = 0.117$ , Fig. 4) using the fixed-effects model (heterogeneity test:  $Q = 1.84$ ,  $p = 0.61$ ,  $I^2 < 0.001$ ).

#### 4. Discussion

Body composition is an increasingly important prognostic factor in many illnesses including chronic diseases [49], critical care [50], and the elderly population [51]. There is mounting evidence that body composition has a strong connection to cancer outcomes [2,52]. A variety

Table 2

HRs for overall survival according to tumour type, disease stage and sarcopenia.

	No. of studies	No. of patients	HR	95% CI	p-value
All cancer types	37		1.437	1.32–1.56	<0.001
Type of tumour					<0.001 <sup>a</sup>
HCC	11	2347	2.160	1.54–3.03	<0.001
Pancreaticobiliary	6	904	1.293	0.98–1.70	0.066
Gastroesophageal	4	649	1.504	1.08–2.08	0.015
Urothelial carcinoma	3	555	1.471	0.99–2.19	0.057
Renal cell carcinoma	3	572	1.748	1.29–2.37	<0.001
Colorectal cancer	3	493	2.247	1.63–3.09	<0.001
Other	7	2259	1.457	1.11–1.91	0.006
Disease stage					<0.001 <sup>a</sup>
Non-metastatic	16	2638	1.538	1.31–1.79	<0.001
Mixed	4	3197	2.045	1.27–3.28	0.003
Metastatic/advanced	17	1944	1.372	1.21–1.56	<0.001
Type of analysis					<0.001 <sup>a</sup>
Multivariate	22		1.513	1.35–1.69	<0.001
Univariate	15		1.556	1.24–1.95	<0.001

Abbreviations: HR, hazard ratio; CI, confidence interval; HCC, hepatocellular carcinoma.

<sup>a</sup> p Value for difference in HRs.

of imaging techniques have been used to evaluate skeletal muscle mass including CT imaging, magnetic resonance imaging, and DEXA [53]. For cancer patients, the frequent use of CT imaging for staging, monitoring, and surveillance provides for a novel and readily available source for identifying sarcopenia. Recently, a growing number of retrospective studies have explored the relationship between SMI obtained from CT imaging and outcomes of patients with solid tumours. Most of the studies included in our meta-analysis have been published since 2012 and more than half were published in 2015, highlighting the expanding interest in the prognostic value of SMI in this population. To our knowledge, this is the first meta-analysis to evaluate the association of SMI and clinical outcomes. We included 38 studies comprising 7843 patients with solid tumours and found that a low SMI was associated with poorer OS (HR = 1.44, 95% CI = 1.32–1.56,  $p < 0.001$ ). Additionally, a low SMI was an unfavourable prognostic factor for CSS (HR = 1.93, 95% CI = 1.38–2.70,  $p < 0.001$ ) and CCS (HR = 1.93, 95% CI = 1.38–2.70,  $p < 0.001$ ). Although we did not find a significant association between low SMI and PFS (HR = 1.54, 95% CI = 0.90–2.64,  $p = 0.117$ ), this is most likely attributable to the small sample size of included patients in this subset analysis (4 studies comprising only 118 patients).

In order to investigate the relationship of sarcopenia and cancer outcomes, we also performed an exploratory analysis by cancer stage. We divided the studies into non-metastatic, advanced/metastatic, and mixed

(metastatic and non-metastatic). Within each subgroup of patients with similar cancer stage, sarcopenia had a significant effect. We were particularly surprised to see this effect in patients with non-metastatic malignancies that were treated with curative intent. We should also highlight that many of those non-metastatic malignancies were HCC and gastrointestinal (GI) malignancies such as oesophageal cancer in which the 5-year survival across all stages is less than 20% [54].

The definition of sarcopenia remains controversial and multiple definitions have been used in the literature. Our study allowed for different definitions for sarcopenia and used the definition provided in the individual studies. The cut-off used for defining sarcopenia in females ranged from 29.6 to 41 cm<sup>2</sup>/m<sup>2</sup> and in men from 36 to 55.4 cm<sup>2</sup>/m<sup>2</sup>. The most commonly used definition

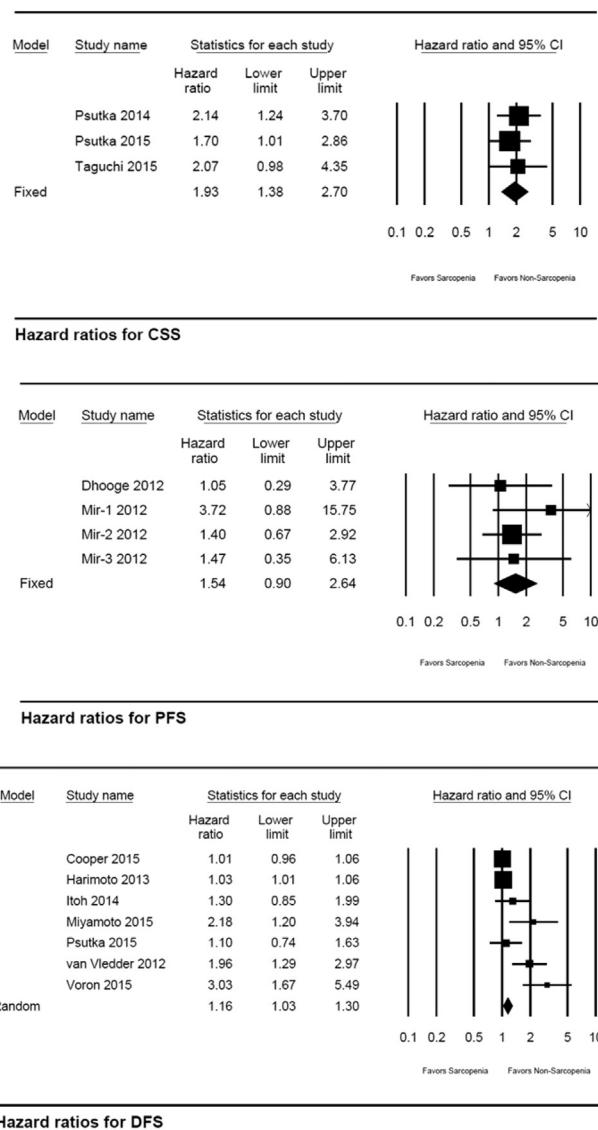


Fig. 4. Forest plots of hazard ratios for various outcomes. Top plot: CSS, cancer-specific survival; middle plot: PFS, progression-free survival and bottom plot: DFS, disease-free survival.

was initially defined by Prado et al. using optimum stratification analysis between low muscle mass and mortality in a population of 250 obese Canadian patients with respiratory or GI malignancies ( $52.4 \text{ cm}^2/\text{m}^2$  for men and  $38.5 \text{ cm}^2/\text{m}^2$  for women) [45]. More recent publications have used cut-offs defined by Martin et al. that also utilised optimal stratification to define thresholds associated with increased mortality and included 1,473 patients (the largest analysis to date) with lung or GI malignancies and incorporated both sex-specific and body mass index (BMI) cut-offs ( $43 \text{ cm}^2/\text{m}^2$  for men BMI <25,  $53 \text{ cm}^2/\text{m}^2$  for men BMI >25, and  $41 \text{ cm}^2/\text{m}^2$  for women regardless of BMI) [13]. Of note, some organisations, including the European Working Group on Sarcopenia in Older People, recommend incorporating both low muscle mass and low muscle function into the definition of sarcopenia [53]. Given that the vast majority of the studies included in this analysis were retrospective; there are limited data on muscle function and future studies are needed to evaluate the association between skeletal muscle mass obtained from cross-sectional CT imaging and physical performance.

The mechanism underlying the relationship of low SMI and poorer outcomes in adults with cancer also remains uncertain. In patients with advanced cancer, the poor outcomes may be related to higher toxicity rates, which in turn, may lead to dose reductions and delivering lower doses of effective cancer treatments [55]. An increased understanding of the underlying mechanisms of muscle loss in adults with cancer is necessary to better develop interventions and treatment strategies. Muscle wasting is the result of a combination of an imbalance between synthetic and degradative protein pathways together with increased myocyte apoptosis and decreased regenerative capacity [56]. Oxidative pathways are also altered in skeletal muscle during muscle wasting and this is likely a consequence of mitochondrial abnormalities that include altered morphology and function, decreased ATP synthesis and uncoupling [56]. Another important role of skeletal muscle is that muscle is a secretory organ of cytokines and other peptides, denominated myokines (interleukin-6 [IL-6], IL-8, IL-15, brain-derived neurotrophic factor, and leukaemia inhibitory factor) that have autocrine, paracrine, or endocrine actions and are extensively involved in inflammatory processes [57].

Recognising the importance of sarcopenia and body composition on outcomes has led to acceleration in research for interventions that can increase or prevent further loss of muscle mass. Many treatments including exercise [58,59], omega-3 fatty acid dietary supplementation [60], and other novel therapeutic approaches including melanocortin-4 receptor antagonists [61], myostatin inhibition [62], beta-blockers, IL-6 antagonism [63], synthetic ghrelin, and vitamin D [64] are being

explored. More prospective research on the impact of these and other interventions are necessary to improve the outcomes of these high-risk patients with cancer.

Our study has several limitations. Firstly, we included the studies evaluating different tumour types, disease stages, therapeutic strategies, and cut-off values of sarcopenia because our goal was to gain general insights into the overall prognostic utility of sarcopenia in patients with solid tumours. More specifically, we included studies of various different tumour types and stages with the largest representation from GI malignancies, including HCC, pancreaticobiliary cancer, and oesophageal cancer. These malignancies have significantly worse cancer outcomes compared with other gender-related malignancies such breast and prostate cancer. Secondly, we used definitions of sarcopenia as defined in the individual studies as no uniformly agreed upon definition for sarcopenia exists. These differences in the definition of sarcopenia likely lead to the significant heterogeneity between the studies and the association of sarcopenia with OS and DFS. To take this into account, we used a random-effects model for these analyses and performed the pre-specified subgroup analyses. Thirdly, most of the studies included in our analysis were retrospective, thus limiting our conclusions. Finally, evidence of publication bias was observed with fewer small studies reporting negative results than would be expected. However, a cumulative meta-analysis plot of OS did not show a shift in the cumulative effect size after adding smaller studies (Supplement 1). This suggests that our results were not biased by smaller studies.

Our meta-analysis confirms the results of smaller studies that show a strong association of sarcopenia and poorer survival among different cancer types and stages. Larger studies of the effect of sarcopenia are needed especially in breast and prostate cancer as well as in haematologic malignancy. The wide use of CT scanning provides investigators with a tool to further explore the association of sarcopenia, its causes, and its association with treatment outcomes. Trials exploring interventions to reverse sarcopenia and how such interventions might improve outcomes are needed.

#### Conflict of interest statement

None declared.

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## Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.ejca.2015.12.030>.

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