


Computed tomography-defined low skeletal muscle index and density in cancer patients: observations from a systematic review

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Abstract

Background Computed tomography (CT) analysis of body composition has garnered interest as a potential prognostic tool in those with cancer. A range of pre-defined thresholds currently exist within the literature to define low skeletal muscle mass and density. The aim of the present systematic review was to assess the prevalence of low skeletal muscle index (SMI) and density (SMD) within the literature, across a range of common solid tumours.

Methods A systematic search of PubMed was carried out to identify studies reporting CT analysis of SMI and SMD in patients with colorectal, oesophageal, gastric, hepatobiliary, pancreatic, breast, and lung cancer. The type of cancer, whether curative or non-curative disease, the anthropomorphic parameter studied, threshold used to define low SMI and SMD, and the prevalence of these anthropomorphic measurements within the population were recorded.

Results Of the 160 studies included, 156 reported an assessment of SMI and 35 reported assessment of SMD. The median prevalence of low SMI was 43% (30.1–57.1) and low SMD 49.4% (31.7–58.5) across the entire cohort. There was little variation in the prevalence of low SMI and SMD when studies were divided into curative and non-curative cohorts—40.7% (27.5–51.3) vs. 48.4% (30.9–60.1) and 37.8% (32.2–52.2) vs. 55.3% (38.5–64.7) respectively. When divided into colorectal, oesophageal, gastric, hepatobiliary, pancreatic, breast and lung cancers, similar prevalence of low SMI (46.0%, 49.8%, 35.7%, 41.1%, 32.3%, 34%, and 49.5%) and low SMD were also observed (52.1%, 54.3%, 71.2%, 56.8%, 55.3%, and 52.6%). This was maintained when studies were stratified into cohorts by threshold used—low SMI (Martin 48.9%, Prado 49.9%, and Others 36.0%) and low SMD (Martin 52.4% and Others 48.6%).

Conclusions Low SMI and SMD are endemic across a range of cancer types and disease stage, challenging pre-existing dogma of the determinants of prevalence.

Keywords Cancer; Body composition; CT

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Introduction

One in two people born in the UK after 1960 will be diagnosed with cancer during their lifetime.¹ In an age of precision medicine, factors that aid prediction of clinical outcomes in patients with cancer are vital in determining the modality and extent of treatment. Body composition analysis

using computed tomography (CT) has garnered considerable interest with regards to its utility in predicting likely outcome. Within the last decade, there has been a substantial volume of research exploring the relationship between skeletal muscle volume² and density,³ and outcomes in patients with operable and advanced cancers across a breadth of histological subtypes and treatment modalities. The expansion in the

number of studies of CT-based body composition analysis and outcomes is attributable to the importance of body composition, the routine use of CT in the staging of tumours, and advances in computer software to carry out such analysis.⁴

In particular, skeletal muscle mass and density have been shown to be consistently associated with poor outcome in patients with cancer.^{2,3} Skeletal muscle mass is most often calculated from the cumulative volume of the intra-abdominal musculature on a CT image slice, generally at the level of the third lumbar vertebra, normalized by the square of the patient's height in metres (skeletal muscle index, SMI), analogous to that of BMI. A range of pre-defined thresholds have been proposed in studies from various populations,^{5–8} although, at present, there are no universal thresholds in use.

The skeletal muscle density (SMD) can also be derived from the CT image slice. However, the basis of the SMD measurement is less clear than that of SMI because unlike SMI, SMD is a measurement unique to the CT image.⁹ In theory, striated skeletal muscle, free from fat infiltration, should have a greater density on CT analysis compared against that with fat deposition.^{10,11} Within the literature, low SMD is defined by a mean muscle attenuation below an established threshold, usually at the level of the third lumbar vertebra, and measured in Hounsfield units (HU). Similar to that of the assessment of the SMI, pre-determined thresholds have been established from studies conducted across a range of populations; however, again, no universally used thresholds exist for the defining of low SMD.^{6,8,12}

A lack of universally used thresholds for the determination of low SMI and SMD is just one of the limitations of CT analysis of body composition parameters for prognostication. With a variety of thresholds in use, interpretation of the external validity of results and comparison becomes difficult. Nevertheless, recent studies have demonstrated excellent inter-observer and intra-observer agreement across a range of software packages in both those with¹³ and without cancer.¹⁴ Therefore, despite the limitations associated with CT-derived SMI and SMD measurements, they provide a routine clinically available objective measure and offer the potential for unique insight into the relationship between the tumour and host. The aim of the present systematic review was to assess the prevalence of low SMI and SMD, taking into account currently established thresholds for these CT-derived analysis and tumour stage in a range of common solid tumours.

Patients and methods

The protocol for this systematic review was developed using PRISMA guidelines.¹⁵ A systematic search of PubMed was carried out to identify studies reporting CT analysis of SMI and SMD in patients with cancer. The search was carried out using

the following MESH terms: 'body composition', 'computed tomography (CT)', 'cancer', 'skeletal muscle', 'skeletal muscle index', 'skeletal muscle density', 'sarcopenia', 'myosteatosis', and 'cachexia'. The search was conducted from the start of the relevant database to the 30th of August 2020. Reference lists from studies of relevance were then hand-searched for any other eligible studies. All relevant studies assessing the relationship between CT analysis of skeletal muscle mass and density, with outcomes in the chosen cancer groups, were included. Conference abstracts, non-English language studies, as well as meta-analyses and systematic reviews were excluded. Studies were then individually screened for relevance based on title alone, prior to review of abstracts, and later, full texts (J. M.). The type of cancer, whether curative or non-curative, the anthropomorphic parameter studied, threshold used to define low SMI and SMD, and the prevalence of these anthropomorphic measurements within the population were recorded. Studies included in the curative cohort were those with patients who had TNM Stages I–III disease treated with curative intent. Studies involving patients with unresectable disease, TNM Stage IV disease or those that examined at metastases were included in the non-curative cohort. Any issues relating to the interpretation of significance or discrepancies in validity of results within the individual studies, were addressed by re-examination with a senior colleague (R. D. D.) and discussion with the senior author (D. C. M.). The STROBE checklist, a validated methodological quality assessment tool, was then used to assess all eligible studies for quality.¹⁶

Results

A total of 1225 studies were identified on initial search of the PubMed database. Following the exclusion of duplicates by the screening of titles, 1163 abstracts were reviewed. There were 321 full papers deemed suitable for review, with 160 meeting inclusion criteria for qualitative analysis (*Figure 1*). A total of 161 records identified did not meet the eligibility criteria and were therefore excluded. Studies were excluded from qualitative analysis for the following reasons: their being systematic reviews and meta-analyses, using total psoas area for calculation of SMI, using CT analysis of vertebral level other than L3 for calculation of total muscle area, those that did not report an SMI (cm²/m²) or SMD (HU), as well as studies that did not publish thresholds used in determination of low SMI and SMD.

Qualitative analysis

There were 42 063 patients were included in the 160 studies selected for qualitative analysis. Of these studies, 156 ($n = 37\,527$ patients) reported an assessment of SMI alone

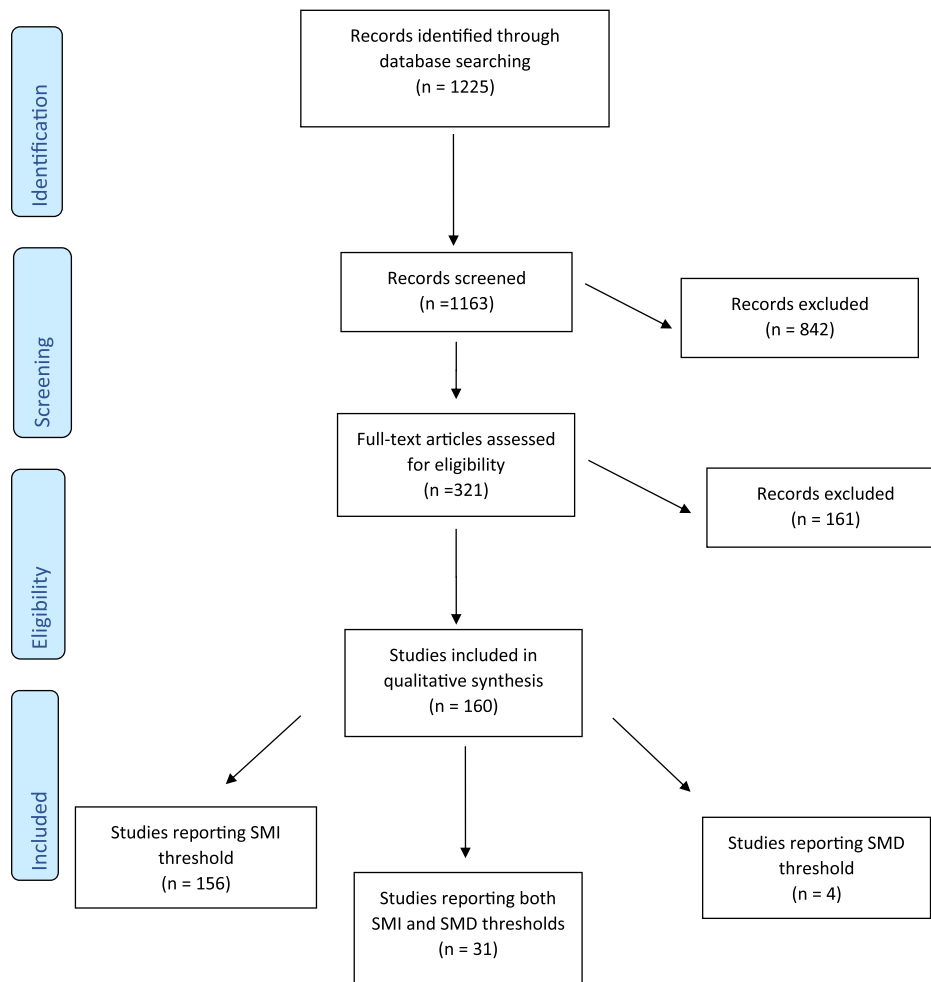


Figure 1 Flow diagram of literature search and included/excluded studies.

using a defined threshold, four studies ($n = 4536$ patients) reported SMD alone using a defined threshold and 31 studies reported both SMI and SMD using defined thresholds ($n = 10\,363$ patients). Prevalences of low SMI and SMD are reported as median (interquartile range).

Skeletal muscle index

Of the 156 studies assessing SMI in cancer patients (refer to *Table S1*), 55.8% ($n = 87$) involved patients with curative disease and 44.2% ($n = 69$) involved patients with non-curative disease. Twenty-five per cent ($n = 39$) used thresholds described by Martin,⁶ 30.1% ($n = 47$) used those described by Prado,⁷ and 44.9% ($n = 70$) reported low SMI using different thresholds (refer to *Table 1*). In studies not using thresholds defined by Martin or Prado (refer to *Table S3*), values for low SMI ranged from ≤ 25.66 ¹⁷ to ≤ 55.4 $\text{cm}^2/\text{m}^{218-20}$ for male patients and ≤ 21.73 ¹⁷ to ≤ 46.4 $\text{cm}^2/\text{m}^{221}$ for female patients.

Table 1 The number of studies and the thresholds used to define low SMI in patients with cancer

| Cancer subtype | Martin | Prado | Other | Total (n) |
|----------------|--------|-------|-------|-----------|
| Colorectal | 15 | 13 | 11 | 39 |
| Oesophageal | 3 | 12 | 11 | 26 |
| Gastric | 7 | 4 | 10 | 21 |
| Hepatobiliary | 2 | 4 | 20 | 26 |
| Pancreatic | 6 | 7 | 10 | 23 |
| Breast | 3 | 5 | 4 | 12 |
| Lung | 2 | 2 | 5 | 9 |
| Total (n) | 38 | 47 | 71 | 156 |

One study by Aleixo *et al.* reported the proportion of patients low SMI across multiple thresholds.²² An SMI below the defined threshold was reported in 40.2% ($n = 15$, 103 patients). Across the entire cohort, the median proportion of patients with low SMI was 43% (30.1–57.1). In those studies of patients with curative cancer, the median low SMI was 40.7%

Table 2 The percentage prevalence of low skeletal muscle index by threshold used

| | Overall | Martin | Prado | Other |
|--------------|-------------------|-------------------|-------------------|-------------------|
| All | 43.0% (30.1–57.1) | 48.9% (33.1–58.7) | 49.9% (39.4–60.2) | 36.0% (21.3–50.1) |
| Curative | 40.7% (27.5–51.3) | 42.9% (30.6–49.9) | 56.7% (43.7–65.3) | 32.9% (24.6–41.5) |
| Non-curative | 48.4% (30.9–60.1) | 54.1% (46.2–60.6) | 47.7% (39.4–60.1) | 47.9% (21.3–63.3) |

Table 3 The number of studies and the thresholds used to define low skeletal muscle density in patients with cancer

| Cancer subtype | Martin (n) | Other (n) | Total (n) |
|----------------|------------|-----------|-----------|
| Colorectal | 7 | 5 | 12 |
| Oesophageal | 2 | 1 | 3 |
| Gastric | 1 | 1 | 2 |
| Hepatobiliary | 0 | 4 | 4 |
| Pancreatic | 3 | 4 | 7 |
| Breast | 3 | 2 | 5 |
| Lung | 1 | 1 | 2 |
| Total (n) | 17 | 18 | 35 |

(27.5–51.3) compared with 48.4% (30.9–60.1) in studies of patients with non-curative disease. With regard to the prevalence of low SMI across the entire cohort, using specific thresholds, median values were similar in studies using thresholds described by either Martin or Prado, 48.9% (37.1–59.3) and 49.9% (39.4–60.2), respectively. However, low SMI was less prevalent in studies using other thresholds at 36.0% (21.3–50.1; refer to *Table 2*). This was likely representative of these studies using threshold values lower than that of both Martin and Prado; meaning less patients would be classified as having low SMI.

Skeletal muscle density

Skeletal muscle density was assessed using defined thresholds in a total of 35 studies (refer to *Table 3*). Of the 35 studies reporting SMD, 37% ($n = 13$) used contrast enhanced CT imaging, while just 6% ($n = 2$) reported that non-contrast scans were used. The remaining 57% ($n = 20$) of studies did not disclose whether contrast enhanced scans were used to determine SMD (refer to *Table S2*). A low SMD was identified in 48.6% ($n = 5038$) of patients, from the 31 studies assessing both SMI and SMD. In the four studies analysing SMD alone, 29.0% ($n = 1316$) of patients were reported as having an SMD below the threshold used. 48.5% ($n = 16$) of studies

assessing SMD used threshold values described by Martin *et al.*⁶ to stratify patients into those with low and high SMD. In the remaining 17 studies assessing SMD, threshold values used ranged from ≤ 22.0 HU²³ to ≤ 44.4 HU^{24–26} in male patients and ≤ 23.5 ²³ to ≤ 39.3 ²⁴ in female patients. Similar to their analysis of SMI, Aleixo *et al.* reported the proportion of patients with low SMD across multiple thresholds.²³ Across the whole cohort, the prevalence of low SMD was 49.4% (31.7–58.5). The median percentage of patients with low SMD was higher in those in the non-curative cohort than in the curative cohort: 55.3% (38.5–64.7) and 37.8% (32.2–52.2), respectively. When comparing studies using the thresholds for low SMD defined by Martin *et al.* with studies using other thresholds, the prevalence of low SMD was similar, at 52.4% (37.5–58.8) and 48.6% (33.3–53.5), respectively (refer to *Table 4*).

Cancer specific analysis

Colorectal

The largest volume of studies assessing skeletal muscle volume and density involved those with colorectal cancer ($n = 39$ studies). There were 13 589 patients included in these 39 studies; 23 of which were constituted by those with curative disease, with 16 involving patients with non-curative disease. Thresholds described by either Martin or Prado were used to define low SMI in 15 (nine curative and six non-curative) and 13 (six curative and seven non-curative) studies, respectively. The remaining 11 studies used other thresholds to classify patients into low and high SMI cohorts (refer to *Table 1*). Threshold values for SMI ranged from ≤ 32.5 ²⁷ to ≤ 54.0 ²⁸ in male patients and ≤ 28.6 ²⁷ to ≤ 42.1 ²⁹ in female patients. Across the whole cohort of patients with colorectal cancer, the prevalence of low SMI was 46.0% (32.3–59.8). When assessing the curative cohort, the median percentage of patients with low SMI was 41.1% (29.1–55.1) compared with 49.1% (42.6–60.8) in the non-curative cohort (refer to *Table 5*). With reference to patients with low SMI across

Table 4 The percentage prevalence of low skeletal muscle density by threshold used

| | Overall | Martin | Other |
|--------------|-------------------|-------------------|-------------------|
| All | 49.4% (31.7–58.5) | 52.4% (37.5–58.8) | 48.6% (33.3–53.5) |
| Curative | 37.8% (32.2–52.2) | 40.7% (27.5–51.3) | 42.9% (30.6–49.9) |
| Non-curative | 55.3% (38.5–64.7) | 48.4% (30.9–60.1) | 54.1% (46.2–60.6) |

Table 5 The percentage prevalence of low skeletal muscle index by cancer type

| Cancer subtype | Overall cohort | Curative | Non-curative |
|----------------|-------------------|-------------------|-------------------|
| Colorectal | 46.0% (32.3–59.8) | 41.1% (29.1–55.1) | 49.1% (42.6–60.8) |
| Oesophageal | 49.8% (39.6–61.5) | 47.9% (34.3–60.7) | 52.9% (47.4–62.0) |
| Gastric | 35.7% (22.9–42.9) | 29.2% (15.8–36.1) | 47.9% (36.9–63.8) |
| Hepatobiliary | 41.1% (30.6–58.7) | 46.5% (40.5–57.8) | 34.8% (15–59) |
| Pancreatic | 32.3% (22.1–48.6) | 32.5% (24.5–47.4) | 63.4% (57.2–64.9) |
| Breast | 34.0% (16.4–42.2) | 25.6% (13.6–35) | 49.0% (36.4–60.2) |
| Lung | 49.5% (42.2–60.9) | 42.2% (37.8–55.5) | 50.3% (47.6–58.4) |

Table 6 The percentage prevalence of low skeletal muscle index by threshold used in those with colorectal cancer

| | Overall | Martin | Prado | Other |
|--------------|-------------------|-------------------|-------------------|-------------------|
| All | 46.0% (32.3–59.8) | 50.4% (44.0–59.8) | 47.7% (39.4–60.2) | 27.5% (24.7–42.3) |
| Curative | 41.1% (29.1–55.1) | 49.8% (31.5–59.8) | 53.8% (42.8–60.1) | 26.6% (24.8–34.5) |
| Non-curative | 49.1% (42.6–60.8) | 54.1% (47.9–58.9) | 43.7% (39.2–58.5) | 46.8% (19.4–63.9) |

Table 7 The percentage prevalence of low skeletal muscle density by threshold used in those with colorectal cancer

| | Overall | Martin | Other |
|--------------|-------------------|-------------------|--------------------|
| All | 52.1% (29.6–64.1) | 52.1% (35.0–67.5) | 29.6% (27.4–52.5) |
| Curative | 52.1% (31.2–53.5) | 45.4% (36.9–60.9) | 41.1% (29.1–52.8) |
| Non-curative | 44.5% (23.4–65.9) | 64.2% (41.8–67.5) | 24.7% ^a |

^aCohort with a solitary study.

specific thresholds, the prevalence in both curative and non-curative studies was 50.4% (44.0–59.8) in those using Martin's parameters, 47.7% (39.4–60.2) in those using Prado's thresholds, and 27.5% (24.7–42.3) in studies using other thresholds. This would suggest that patients with colorectal cancer were more likely to be considered to have low skeletal muscle volume in studies using the thresholds described by Martin. When comparing curative and non-curative studies, the prevalence of low SMI was 49.8% (31.5–59.8) compared with 54.1% (47.9–58.9) in studies using Martin's thresholds, 53.8% (42.8–60.1) compared to 43.7% (39.2–58.5) in studies using Prado's threshold, and 26.6% (24.8–34.5) compared with 46.8% (33.1–55.4) in studies using other thresholds. When assessing curative and non-curative cohorts, one might expect those with curative disease to have higher skeletal muscle volume, as reflected by studies using the thresholds described by Martin. However, the inverse of this was demonstrated in studies using thresholds described by Prado, where low SMI was more prevalent in the curative cohort (refer to *Table 6*).

A total of 12 studies composed of 7154 patients with colorectal cancer assessed SMD using CT (refer to *Table 3*). Of these studies, 75% ($n = 8$) were composed of those with curative disease and 25% ($n = 4$) had non-curative disease. Seven studies (four curative and three non-curative) used the thresholds described by Martin to define low SMD. In the remaining five studies that examined SMD in those with colorectal cancer, four included patients with curative disease

and one study included those with non-curative disease. The thresholds used to define low SMD ranged from $\leq 22.0^{23}$ to $\leq 38.2^{30}$ HU in male patients and $\leq 23.5^{23}$ to ≤ 33.6 HU³⁰ in female patients. Across the whole cohort of patients with colorectal cancer, the median percentage of those with a low SMD was 52.1% (29.6–64.1). When assessing the curative cohort, the median percentage of patients with low SMD was 52.1% (31.2–53.5) compared with 44.5% (23.4–65.9) in the non-curative cohort (refer to *Table 7*). When examining specific thresholds, the median percentage of patients with low SMD using thresholds defined by Martin *et al.* was 52.1% (35.0–67.5), and 29.6% (27.4–52.5) in the cohort using other thresholds (refer to *Table 7*).

Oesophageal

Twenty-six studies, comprised of 4205 patients, reported CT analysis of SMI and SMD in patients with oesophageal cancer (refer to *Table 1*). All 26 studies reported the proportion of patients with low SMI determined by defined indices, with three studies also assessing SMD. One study included male-only patients in their cohort for analysis.³¹ Of the studies, 69.2% ($n = 18$) included patients with curative disease with the remaining 30.8% ($n = 8$) comprising of patients with non-curative cancer. Twelve studies (46.2%) assessed SMI using thresholds described by Prado *et al.*,⁷ with only 11.5% ($n = 3$) using thresholds described by Martin *et al.*⁶ The remaining 42.3% ($n = 11$) of studies used other thresholds to define low SMI. Thresholds used to define low SMI ranged

from $\leq 43.1^{32}$ to $\leq 55^{33-36}$ in male patients and $\leq 32.7^{32}$ to $\leq 41.1^{37}$ in female patients. Across the entire cohort, the prevalence of low SMI was 49.8% (39.6–61.5). With regard to curative and non-curative cohorts, prevalence of low SMI was similar with 47.9% (34.3–60.7) and 52.9% (47.4–62.0), respectively (refer to Table 5). Similar median percentages of those with low SMI were also observed when comparing studies using Prado's thresholds to the studies using other threshold values: 49.4% (34.4–57.4) and 50.1% (35.7–70.4), respectively (refer to Table 2).

Of the studies, 11.5% ($n = 3$) identified also analysed SMD using defined thresholds.^{32,38,39} Two of these studies used thresholds described by Martin to define low SMD: one with curative cancer patients and the other non-curative. The remaining study used an alternative threshold to Martin (male patients ≤ 35.9 , female patients ≤ 24.8) to determine low SMD in non-curative oesophageal cancer patients (refer to Table 3).

Gastric

Twenty-one studies, which assessed low SMI using defined thresholds across a total of 4774 patients with curative and non-curative gastric cancer, were included in the qualitative analysis (refer to Table 1). Two of these studies also assessed low SMD using defined thresholds^{26,40} (refer to Table 3). There were 66.7% ($n = 14$) of studies of patients with curative disease, with 33.3% ($n = 7$) analysing those with non-curative cancer. Seven studies (33.3%) used thresholds described by Martin *et al.* to define low SMI, and 19% ($n = 4$) used those described by Prado. The remaining 47.6% ($n = 10$) studies used alternative thresholds. Threshold values ranged from $\leq 32.5^{27}$ to $\leq 49.0^{41}$ in male patients and $\leq 28.6^{27}$ to $\leq 34.9^{26,42-44}$ in female patients. Across the entire cohort, the prevalence of low SMI was 35.7% (22.9–42.9) in those with gastric cancer. A higher median percentage was present in studies of non-curative disease, 47.9% (36.9–63.8), compared to those of curative disease, at 29.2% (15.8–36.1) (refer to Table 5). A similar variation in the prevalence of low SMI was also observed when individual thresholds were analysed. In studies using thresholds described by Martin and Prado, the median percentage of patients with low SMI was 41.8% (33.2–50.3) and 39.8% (36–43.5), respectively. Studies using other

thresholds were noted have a lower prevalence of low SMI, with a median percentage of 21.1% (13.2–29.4) (refer to Table 2).

Two studies (9.5%) reported low SMD using defined indices. One study assessed SMD in a non-curative cohort using thresholds described by Martin *et al.* The other study used alternative thresholds to assess low SMD (refer to Table 3).

Hepatobiliary

There were 5265 patients included in the 26 studies assessing skeletal muscle volume using CT in those with hepatobiliary malignancies (refer to Table 1). Of these 26 studies, 15.4% ($n = 4$) also assessed SMD. 34.6% ($n = 9$) studies included patients with curative disease, with 65.4% ($n = 15$) comprising of those with non-curative cancer. One study included a cohort of male-only patients undergoing treatment for non-curative hepatobiliary cancer.⁴⁵ Most studies, 76.9% ($n = 20$), used thresholds other than those described by either Martin or Prado to define low SMI. Thresholds used ranged from $\leq 36^{46}$ to $\leq 55.4^{19}$ in male patients and $\leq 29.6^{21}$ to $\leq 46.4^{25}$ in female patients. Only 15.4% ($n = 4$) of studies used thresholds described by Prado to define low SMI, and just 7.7% ($n = 2$) used those described by Martin *et al.* (refer to Table 2). Across the entire cohort, the prevalence of low SMI was 41.1% (30.6–58.7). Surprisingly, the median percentage of those with low SMI was less in the non-curative cohort than in the curative disease cohort: 34.8% (15.0–59.0) compared with 46.5% (40.5–57.8) (refer to Table 5). This is likely related to the majority of studies in the non-curative cohort using different thresholds to those described by either Martin or Prado and is supported by the median percentage of those with low SMI in the alternative-threshold cohort being similar, at 37.6% (26.6–60.1) (refer to Table 1).

Four studies that comprised of 1632 patients assessed SMD in those with hepatobiliary cancers (refer to Table 3). Three studies included those with non-curative disease and the remaining study included patients with curative cancer. All four studies used thresholds other than those described by Martin *et al.* The prevalence of low SMD across the entire cohort was 56.8% (48.6–70.0) (refer to Table 8).

Table 8 The percentage prevalence of low skeletal muscle density by cancer type

| Cancer subtype | Overall cohort | Curative | Non-curative |
|----------------|-------------------|--------------------|--------------------|
| Colorectal | 52.1% (29.6–64.1) | 52.1% (31.2–53.5) | 44.5% (23.4–65.9) |
| Oesophageal | 54.3% (52.1–56.4) | 58.5% ^a | 50.0% ^a |
| Gastric | 71.2% (64.9–77.6) | 83.9% ^a | 58.5% ^a |
| Hepatobiliary | 56.8% (48.6–70.0) | 48.8% ^a | 65.0% (56.8–75.0) |
| Pancreatic | 55.3% (24.7–64.2) | 44.5% (23.4–65.9) | 55.3% |
| Breast | 52.6% (36.8–59.6) | 36.8% (35.4–44.7) | 72.8% (66.2–79.4) |
| Lung | 19.3% (14.7–23.8) | NR | 19.3% (14.7–23.8) |

^aCohort with a solitary study.

No studies reported skeletal muscle density in patients with curative lung cancer.

Pancreatic

A total of 4689 patients were included in the 23 studies that used CT imaging to analyse SMI in those with curative and non-curative pancreatic cancer (refer to *Table 8*). Of the 23 studies included in the qualitative analysis, 26.1% ($n = 6$) also assessed SMD using defined thresholds.^{47–50} A further study analysing SMD in isolation, using a defined threshold, was also included.⁵¹ Of the studies assessing SMI, 30.4% ($n = 7$) used the thresholds described by Prado, with 26.1% ($n = 6$) using those described by Martin *et al.* The remaining 43.5% ($n = 10$) of studies used thresholds of different values. Thresholds used in these studies ranged from ≤ 36.2 ⁵² to ≤ 55.4 ²⁰ in male patients and from ≤ 29.6 ⁵² to ≤ 38.9 ^{18,20} in female patients. Across the entire cohort, the prevalence of low SMI was 32.3% (22.1–48.6). A higher prevalence of low SMI was presented in the non-curative cohort, at 63.4% (57.2–64.9), in comparison with only 32.5% (24.5–47.4) in the curative patient cohort. A range in the prevalence of low SMI was also noted when analysing cohorts of studies using specific thresholds (refer to *Table 5*). Studies using thresholds described by Prado *et al.* had a median percentage of patients with low SMI of 63.4% (57.2–64.9). This was the highest of all specific thresholds, with studies using Martin *et al.*'s parameters having a median percentage of 49.8% (31.3–57.9), and those in the other threshold cohort have a median percentage of 32.3% (22.1–48.6). This can be attributed to the majority of studies using Prado's thresholds being comprised of patients with non-curative disease, hence the similar median percentages. This was also the case in studies using thresholds other than those described by either Prado or Martin mainly involving those patients with curative disease (refer to *Table 2*).

Seven studies involving 1539 patients assessed SMD in those with pancreatic cancer using CT imaging (refer to *Table 3*). Of the studies, 85.7% ($n = 6$) involved those with curative disease. Three studies used thresholds described by Martin *et al.*⁶ to define low SMD, with the remaining four studies using different thresholds. Across the entire cohort, the prevalence of low SMD was 55.3% (24.7–64.2) (refer to *Table 8*).

Breast

Twelve studies comprising of 4889 female patients with breast cancer were identified and included in the qualitative analysis (refer to *Table 1*). Of the studies, 66.7% ($n = 8$) included those with curative disease, with the remaining four studies including those with non-curative disease. 41.7% ($n = 5$) of studies used thresholds described by Prado *et al.* to assess low SMI and 25% ($n = 3$) used those described by Martin *et al.* The remaining 33.3% ($n = 4$) used thresholds of $< 40 \text{ cm}^2/\text{m}^2$. Across the entire cohort, the prevalence of low SMI was 34% (16.4–42.2). A lower median percentage was noted in those with curative disease, with 25.6% (13.6–35.0) having low SMI, compared with non-curative

disease, with a median percentage of 49% (36.4–60.2) patients having low SMI (refer to *Table 5*).

Five studies were identified, comprising of 4036 patients in total, that assess SMD in those patients with breast cancer (refer to *Table 3*). Three of the studies assessed those with curative disease and the other two studies examined those with non-curative breast cancer. Thresholds for low SMD described by Martin *et al.* were used in three studies. The remaining two studies used ≤ 37.8 HU as the threshold to define those with low SMD. Across the entire cohort, the prevalence of low SMD was 52.6% (36.8–59.6) (refer to *Table 8*).

Lung

Nine studies were identified which met the inclusion criteria; involving 1586 patients, they used CT imaging to assess skeletal muscle in those with lung cancer (refer to *Table 1*). Three studies included individuals with curative disease, with six including patients with non-curative or palliative lung cancer. One study included a cohort of male-only patients.⁵³ Two studies used the thresholds described by either Martin or Prado to define low SMI respectively. The remaining five studies used thresholds ranging from ≤ 25.63 ²⁵ to ≤ 55 ⁵⁴ in male patients, and from ≤ 21.73 ¹⁷ to ≤ 41.1 ⁵⁵ in female patients. Across the entire cohort, the median percentage of those with low SMI was 49.5% (42.2–60.9) (refer to *Table 5*).

Two studies assessed SMD in those with lung cancer. Both studies involved those with non-curative disease (refer to *Table 3*). One study used thresholds described by Martin *et al.* to define low SMD.⁵⁶ The other study used a threshold of ≤ 28 HU in male patients and ≤ 23.8 in female patients.⁵³

Discussion

The present systematic review included 160 studies, including more than 42 000 patients, that used CT imaging to determine SMI and SMD in patients with cancer. In this substantial cohort it was of interest that both a low SMI and a low SMD had a percentage prevalence between 35% and 50% and that this was similar irrespective of threshold used, tumour type, and stage of disease. Therefore, it would appear that poor muscle quantity and quality are endemic in patients with cancer and that such poor muscle status occurs at diagnosis.

There is now a substantial literature that shows the detrimental impact that low SMI and SMD have on survival outcomes of patients with cancer.^{2,3} However, in the present review, low skeletal muscle mass (and density) had similar prevalence across cancer types. Given that there is wide variation in survival across cancer types this would suggest that body composition is not the main determinant of survival. It may be that the prognostic value of SMI reflects its measure of the nutritional and functional reserve of the cancer patient and that this reserve is eroded by the magnitude of the

immune/inflammatory challenge posed by the tumour to the host. Indeed, previous studies have shown that systemic inflammatory response is associated with a more aggressive tumour type and⁵⁷ low SMI and SMD on CT analysis⁵⁸ and survival.^{59,60} It is therefore imperative that body composition be used in conjunction with other factors, such as systemic inflammation, to stage the host, as well as staging of the tumour.⁶¹

Patients with cancer often experience anorexia, loss of weight and skeletal muscle mass as the cancer progresses, and systemic inflammation.⁶² This is termed cancer cachexia and has been shown to be associated with poorer outcomes. Despite the impact cancer cachexia has on outcomes for patient with cancer, the pathogenesis for the changes in body habitus is not clearly understood.⁶³ Patients with certain cancers, such as lung and gastrointestinal, are often thought of as having higher losses of weight and skeletal muscle mass. However, the results of this systematic review clearly show that low SMI and SMD are endemic across all cancer types, present in both curative and non-curative cohorts (refer to *Tables 5 and 8*). This is made evident in comparison of prevalence of low SMI in curative colorectal cancer studies using Prado's thresholds, 53.8% (42.7–60.1), with those in studies of patients with curative oesophageal cancer 47.2% (30.1–60.1) or non-curative pancreatic cancer 63.9% (59.8–65.1) using the same thresholds. The results of this systemic review challenge the perceived phenotype hypothesized for individuals with specific cancers. This in turn suggests that body composition may only be one of number of factors determining the outcome of those with cancer.

There are several limitations of this systematic review. First, the studies included were mainly retrospective with implications for the introduction of sample bias. However, the effect of this is likely to be minimized due to the volume of studies included. Second, heterogeneity existed across the included studies with a range of threshold values used to define low SMI and SMD. Specifically, nearly half of all studies reporting assessment of SMI included used a threshold other than those described by Martin or Prado *et al.* Similarly, nearly half of the studies assessing SMD used thresholds other than those described by Martin *et al.*, limiting comparison and subsequent comment on overall prevalence of muscle status. However, when comparing just these threshold values, the median overall prevalence of low SMI was 49% and 50%, respectively. Furthermore, when these studies were stratified by curative and non-curative disease, there was little variation in the prevalence of low SMI (43% vs. 57%) and (54% vs. 48%), respectively (shown in *Table 2*). Nevertheless, universal thresholds will be required to reliably determine the prevalence of low SMI and SMD in patients with cancer and allow for future investigation of the effect of body composition parameters on outcomes. Third, although the majority of studies assessing SMI reported the vertebral level analysed, calculation used and the normalization, over half of the included studies (57%)

assessing SMD failed to report important technical considerations such as which phase of CT scan the image used to determine the mean muscle attenuation was taken. This has the potential to introduce further confounding variables into the methodology and supports the argument for standardized protocols. Finally, age-related sarcopenia (age at cancer diagnosis) is a potential confounding variable in the present analysis. Since Martin *et al.* provided thresholds for both SMI and SMD, age was compared in the Martin studies ($n = 38$), across the curative ($n = 21$), and non-curative cohorts ($n = 17$). This analysis showed that the mean age was similar in the curative and non-curative cohorts (64 ± 8 and 62 ± 5 years, respectively) and therefore unlikely to be a major confounding factor in the present analysis. Nevertheless, it will be important to carry out analysis in multiple tumour types and stages of disease using the same methodology to eliminate the above potentially important confounding factors and to confirm the present observations.

In conclusion, low SMI and SMD are endemic across a range of cancer types and disease stage. To date, there has been a belief that skeletal muscle parameters differ between cancers which are curable vs. more advanced stages. The findings herein challenge this belief with levels of prevalence observed. Further multicentre studies are required to produce international disease-specific thresholds for clinically relevant CT analysis of body composition.

Conflict of interest

No conflicts of interest to declare.

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The following manuscript complies with the ethical guidelines for authorship and publishing of the Journal of Cachexia, Sarcopenia and Muscle.⁶⁴

Online supplementary material

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Studies reporting CT analysis of Skeletal Muscle Index.

Table S2. Studies reporting CT analysis of Skeletal Muscle Density.

Table S3. Thresholds for skeletal muscle index and density.

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