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REVIEW ARTICLE

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Assessing skeletal muscle radiodensity by computed tomography: An integrative review of the applied methodologies

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Abstract

Low-radiodensity skeletal muscle has been related to the degree of muscle fat infiltration and seems to be associated with worse outcomes. The aim of this study was to summarize the methodologies used to appraise skeletal muscle radiodensity by computed tomography, to describe the terms used in the literature to define muscle radiodensity and to give recommendations for its measurement standardization. An integrative bibliographic review in four databases included studies published until August 2019 in Portuguese, English or Spanish and performed in humans, adults and/or the elderly, of both sex, which investigated skeletal muscle radiodensity through computed tomography (CT) of the region between the third and fifth lumbar vertebrae and evaluated at least two muscular groups. One hundred and seventeen studies were selected. We observed a trend towards selecting all abdominal region muscle. A significant methodological variation in terms of contrast use, selection of skeletal muscle areas, radiodensity ranges delimitation and their cut-off points, as well as the terminologies used, was also found. The methodological differences detected are probably due to the lack of more precise information about the correlation between skeletal muscle radiodensity by CT and its molecular composition, among others. Therefore, until the gaps are addressed in future studies, authors should avoid arbitrary approaches when reporting skeletal muscle radiodensity, especially when it comes to prognosis inference. Studies using both CT and direct methods of muscle composition evaluation are encouraged, to enable the definition and validation of the best approach to classify fat-infiltrated muscle tissue, which will favour the nomenclature uniformization.

KEYWORDS

body composition, muscle fat infiltration, muscle quality, muscle tissue, myosteatosis

1 | INTRODUCTION

Computed tomography (CT) is a commonly used method to investigate skeletal muscle (SM) size and composition (Aubrey *et al*., 2014; Brandberg *et al*., 2008; Goodpaster, Kelley, Thaete, He, & Ross, 2000). Studies have shown that the muscle radiodensity has a direct correlation with the triglyceride content evaluated by muscle biopsy (Aubrey *et al*., 2014), that is the greater the SM fat infiltration, also called myosteatosis, the lower the tissue radiodensity. Hence, CT has recently gained attention as a convenient method to assess

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one of the features of SM quality, which also include morphology, architecture and metabolic function, as it is often available in chronic disease patients, as part of the routine diagnosis or clinical follow-up (Correa-de-Araujo *et al.*, 2017; Fragala, Kenny, & Kuchel, 2015; Goodpaster, Kelley, et al., 2000; Miljkovic & Zmuda, 2010).

Current studies relate several health problems to low SM radiodensity, both in healthy individuals as in different sorts of diseases, triggering, for example, impairment in functional capacity and glycemic control, lower survival, worse surgical outcomes and cancer treatment toxicities (Akahori *et al.*, 2015; Aubrey *et al.*, 2014; Chu *et al.*, 2017; Daly *et al.*, 2017; Hicks *et al.*, 2005b; Komiya *et al.*, 2006; Locke *et al.*, 2017; Martin *et al.*, 2013; Matsumoto *et al.*, 2018; Mayer *et al.*, 1989; Okumura *et al.*, 2017a; Rier *et al.*, 2017; Rollins *et al.*, 2016; Sebro, 2017; Silva de Paula, de Aguiar Bruno, Azevedo Aredes, & Villaça Chaves, 2018; Van Rijssen *et al.*, 2017).

A highly divergence in approaches is observed among CT-based studies, especially regarding the evaluation of different body regions, muscle groups, radiodensity boundaries, contrast agents use and cut-off points (Aubrey *et al.*, 2014). The terminologies used to define low radiodensity are also highly varied: SM attenuation, myosteatosis, low-quality SM, intramuscular adipose tissue and fat infiltrated SM are the most used. The lack of standardization hinders the literature search and the comparison of the studies' results (Anderson *et al.*, 2013; Atlan *et al.*, 2017; DeAndrade, Pedersen, Garcia, & Nau, 2018; Komiya *et al.*, 2006; Mayer *et al.*, 1989).

Previous reviews that summarized the appraisement of SM radiodensity by CT (Aubrey *et al.*, 2014; Daly, Prado, & Ryan, 2018; Kazemi-Bajestani, Mazurak, & Baracos, 2016) did not explore extensively the topics related to the methodological approach in different populations.

Therefore, this integrative literature review aims to summarize the CT-based approaches performed in different health areas for indirect evaluation of SM fat infiltration, to describe the terms used to define muscle radiodensity, as well as give recommendations for its measurement standardization.

2 | METHODS

2.1 | Search strategies

U.S. National Library of Medicine (PubMed), Scopus, Web of Science and Latin American and Caribbean Health Sciences Literature (LILACS) databases were searched between April 2018 and August 2019. Official descriptors were selected from PubMed's Medical Subject Headings and Descriptors in Health Sciences, in addition to free terms of researchers' previous knowledge, pertinent to the research topic, in order to maximize the identification of relevant studies. The process was carried out in English at PubMed, Scopus and Web of Science databases and, in English, Portuguese and Spanish at LILACS database. Moreover, characteristics search methods of each base were also applied.

Aiming a comprehensive literature scan, the search was composed by one conceptual block. Whenever necessary, term truncations and the Boolean operator "OR" for combination of terms were used. Searches comprised title, abstract and keywords, using specific field markers for each database. The complete strategies applied, and the number of studies found in each database is listed in the Table S1.

2.2 | Eligibility criteria

The eligibility criteria were as follows: studies published until August 2019 in Portuguese, English or Spanish; with full-text availability; conducted in humans, addressing adults and/or the elderly of both sex, healthy or sick; originals; observational design (transversal or longitudinal); which investigated SM radiodensity by CT of the region between the third and fifth lumbar vertebrae (L3 and L5), since it is the most adequate method according to the literature and because these specific regions present a high correlation with the total body skeletal muscle mass (Daly *et al.*, 2017; MacDonald, Greig, & Baracos, 2011; Rodrigues & Chaves, 2018; Shen *et al.*, 2004; Silva de Paula *et al.*, 2018); and studies using at least two muscular groups of this anatomical location, since a single SM group is not able to represent the total body musculature (Rutten *et al.*, 2017; van Dijk *et al.*, 2017).

2.3 | Studies selection

For the selection process (Figure 1), the first researcher systematically assessed the eligibility of each study resulting from database searches based on title and abstract reading. The complete selected articles were carefully reviewed by another researcher and compared with those of the initial evaluator. When necessary, the articles were discussed with the study group and eligibility was determined by consensus.

Data of the included studies were computed and refined during the extraction process. For this, a standard form was developed with the information available in the methodology section of the selected articles. This tool included the following information: authors, publication year, population characteristics (age, sex and presence or absence of diseases), selected abdominal region, muscle groups and its areas analysed by CT, radiodensity ranges and methodologies used to set their cut-off points and terms defining SM radiodensity.

3 | RESULTS AND DISCUSSION

The development of the imaging tools has allowed more consistent and precise body composition diagnoses and approaches (Hopkins *et al.*, 2018; Kazemi-Bajestani *et al.*, 2016). This article reviewed the methodologies and terminologies used to appraise CT-based SM

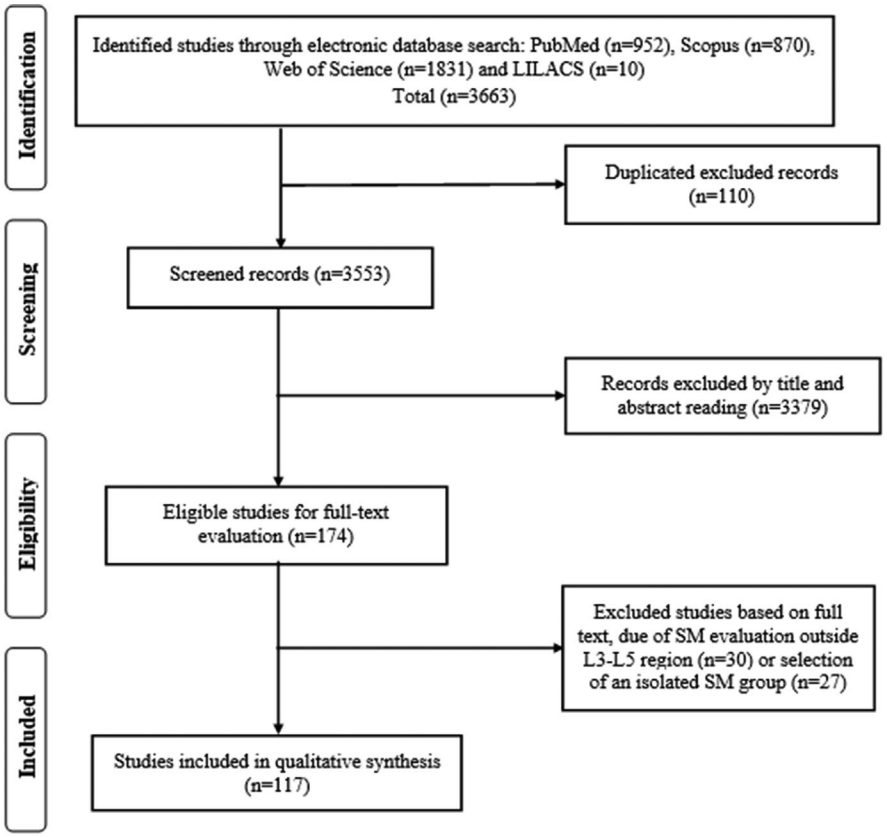

FIGURE 1 Flow diagram of the studies selection process for inclusion in this review. LILACS, Latin American and Caribbean Health Sciences Literature; L3, Third Lumbar Vertebrae; L5, Fifth Lumbar Vertebrae; SM, Skeletal Muscle

radiodensity in different populations. Although one of our aims was to call attention for the variability of the terminologies adopted by the studies, we opted to use the term "SM radiodensity" as a standard term in this review, once it seems to be a more technical definition, as discussed below.

Tables 1, 2, 3 and 4 compile the findings of the 117 included articles. The highly prevalent studies assessing cancer patients (Table 1) were probably due to CT availability, which is performed as a routine for diagnosis, staging and clinical follow-up and, thus, favour its convenient use in such population (Heymsfield, Ross, Wang, & Frager 1997; Daly, Prado, et al., 2018; Hopkins & Sawyer, 2018).

3.1 | Clinical application of muscle radiodensity assessment

Besides the mechanical function performed by SM, it is also involved in metabolic processes, both in health and disease conditions (Erlandson, Lorbergs, Mathur, & Cheung, 2016); therefore, the use of tools to evaluate its composition is of a major importance. For this purpose, the muscle biopsy, being the most invasive option, is available (Goodpaster, Kelley, et al., 2000; Miljkovic & Zmuda, 2010), though less invasive image tools such as CT, magnetic resonance imaging (MRI) (Aubrey *et al*., 2014), dual-energy X-ray absorptiometry (DXA) (Lee, Shin, et al., 2019) and ultrasonography (Ismail *et al*., 2015; Mota & Stock, 2017) can also be used.

CT was initially applied to determine SM composition in healthy, clinical and/or surgical populations, but especially in the elderly. Currently, it has been increasingly used in other pathological conditions (Aubrey *et al*., 2014; Hicks *et al*., 2005b; Kaibori *et al*., 2015; Kuk, Church, Blair, & Ross, 2008; Mayer *et al*., 1989; Torriani, Hadigan, Jensen, & Grinspoon, 2003; Yamashita *et al*., 2017).

CT distinguishes tissues based on their radiodensity, expressed in Hounsfield units (HU), using a linear scale that consider water (0HU) and air (−1000HU) as references (Goodpaster, Kelley, et al., 2000). The method is sensitive to proton content per unit of mass, which is high in adipose tissue (Goodpaster, Kelley, et al., 2000), providing clear radiological findings, including area, volume and radiodensity precise quantification (Daly, Prado, et al., 2018). Such characteristics allow the indirect assessment of the intramuscular adipose tissue.

However, CT is not able to directly measure the lipid amount in muscles neither differentiate the fat deposits location (intra- or extracellular) (Goodpaster, 2002; Karampatos *et al*., 2016; Machann *et al*., 2003). Another limitation is that individuals are not usually submitted to this type of examination exclusively for research purposes or body composition assessment, due to the substantial ionization radiation emitted (MacDonald *et al*., 2011). Factors related to the CT examination can also affect SM radiodensity, such as tube voltage, equipment calibration, slice thickness, contrast agents use and phases (Fuchs *et al*., 2018; van der Werf *et al*., 2018). On the other hand, as mentioned above, this tool

TABLE 1 Characteristics of the populations addressed by the studies

Characteristics	% (*n*)	References
Cancer patients	60.7% (*n* = 71)	1; 2; 3; 4; 5; 6; 7; 8; 9; 10; 11; 12; 13; 14; 15; 16; 17; 18; 19; 20; 21; 22; 23; 24; 25; 26; 27; 28; 29; 30; 31; 32; 33; 34; 35; 36; 37; 38; 39; 40; 41; 42; 43; 44; 45; 46; 47; 48; 49; 50; 51; 52; 53; 54; 55; 56; 57; 58; 59; 60; 61; 62; 63; 64; 65; 66; 67; 68; 69; 70; 71
Healthy individuals	14.5% (*n* = 17)	72; 73; 74; 75; 76; 77; 78; 79; 80; 81; 82; 83; 84; 85; 86; 87; 88
Other patients (critical, in renal and hepatic transplant, pancreatitis, apnoea, seropositive, hypercortisolism and surgical)	10.2% (*n* = 12)	89; 90; 91; 92; 93; 94; 95; 96; 97; 98; 99; 100
CNCD patients (overweight, obesity, diabetes mellitus, hepatic steatosis, cirrhosis, COPD)—excluding cancer	8.5% (*n* = 10)	101; 102; 103; 104; 105; 106; 107; 108; 109; 110
Orthopaedic and neuromuscular disease patients	6% (*n* = 7)	111; 112; 113; 114; 115; 116; 117

Abbreviations: CNCD, Chronic non-communicable diseases; COPD, chronic obstructive pulmonary disease.

1, Antoun *et al.* (2013); 2, Martin *et al.* (2013); 3, Akahori *et al.* (2015); 4, Aust *et al.* (2015); 5, Fujiwara *et al.* (2015); 6, Malietzis *et al.*, (2015); 7, Malietzis*et al.*, (2016); 8, Malietzis, Johns, *et al.* (2016); 9, Malietzis, Lee, *et al.* (2016); 10, Boer *et al.* (2016); 11, Cushen *et al.* (2016); 12, Hayashi *et al.* (2016); 13, Kumar *et al.* (2016); 14, Pędziwiatr *et al.* (2016); 15, Rollins *et al.* (2016); 16, Sjøblom *et al.* (2016); 17, Tamandl, Pedley, Hoffmann, Fox, and Murabito (2016); 18, Atlan *et al.* (2017); 19, Bye *et al.* (2017); 20, Chu *et al.* (2017); 21, Daly *et al.* (2017); 22, Daly, Ní Bhuachalla, et al. (2018); 23, Kubo, Naito, Mori, Osawa, and Aruga (2017); 24, Loumaye *et al.* (2017); 25, Okumura *et al.* (2017a); 26, Okumura *et al.* (2017b); 27, Rier *et al.* (2017); 28, Rier *et al.* (2018); 29, Shachar, Deal, Weinberg, Williams, et al. (2017); 30, Shachar, Deal, Weinberg, Nyrop, et al. (2017); 31, Van Rijssen *et al.* (2017); 32, van Roekel *et al.* (2017); 33, Williams *et al.* (2017); 34, Williams *et al.* (2018); 35, Choi *et al.* (2018); 36, Deng *et al.* (2018); 37, Ní Bhuachalla *et al.* (2018); 38, Rodrigues and Chaves (2018); 39, Silva de Paula *et al.* (2018); 40, Souza *et al.* (2018); 41, Versteeg *et al.* (2018); 42, Charette *et al.* (2019); 43, Kiss et al. (2019); 44, Zhang *et al.* (2018); 45, Dohzono, Sasaoka, Takamatsu, Hoshino, and Nakamura (2019); 46, van Baar *et al.* (2018); 47, Atasevenet et al. (2018); 48, Martin *et al.* (2018); 49, Stretch *et al.* (2018); 50, van Dijk *et al.* (2018); 51, van Vugt, Gaspersz, et al. (2019); 52, van Vugt *et al.* (2018); 53, Silva de Paula, Rodrigues, and Chaves (2019); 54, Kroenke *et al.* (2018); 55, Weinberg *et al.* (2018); 56, Sheean *et al.* (2019); 57, Sueda *et al.* (2018); 58, Brown *et al.* (2018); 59, Caan *et al.* (2018); 60, Chakedis *et al.* (2018); 61, Cortellini *et al.* (2018); 62, da Rocha *et al.* (2019); 63, Dijksterhuis *et al.* (2019); 64, Dolan *et al.* (2019); 65, Grønberg *et al.* (2019); 66, Lee, Lin, et al. (2019); 67, Lin *et al.* (2019); 68, Xiao *et al.* (2019); 69, Xiao *et al.* (2018); 70, Linder *et al.* (2019); 71, McSorley, Black, Horgan and McMillan (2018); 72, Hicks *et al.* (2005a); 73, Hicks *et al.* (2005b); 74, Kalichman, Hodges, Li, Guermazi, and Hunter (2010); 75, Anderson *et al.* (2013); 76, Therkelsen *et al.* (2013); 77, Miljkovic *et al.* (2013); 78, Therkelsen, Pedley, Hoffmann, Fox, and Murabito (2016); 79, Goodpaster, Kelley, et al. (2000); 80, Anderson, Bean, Holt, Keel, and Bouxsein (2014); 81, Iodate et al. (2017); 82, Graffy *et al.* (2019); 83, Vella *et al.* (2018); 84, Maltais *et al.* (2018); 85, van Hollebeke, Cushman, Schlueter, and Allison (2018); 86, van der Werf *et al.* (2018); 87, Lenchik *et al.* (2019); 88, van Vugt, van Putten, et al. (2019); 89, Looijaard *et al.* (2016); 90, Erlandson *et al.* (2017); 91, Locke *et al.* (2017); 92, van Grinsven *et al.* (2017); 93, Matsumoto *et al.* (2018); 94, Bhanji, Narayanan, et al. (2019); 95, Bhanji, Takahashi, et al. (2019); 96, Tachi, Kozuka, Hirai, Ishizu, et al. (2018); 97, Tachi, Kozuka, Hirai, Kojima, et al. (2018); 98, Hong *et al.* (2019); 99, Dusseaux *et al.* (2019); 100, van der Kroft, Bours, Janssen-Heijnen, van Berlo, and Konsten (2018); 101, Komiya *et al.* (2006); 102, Kim *et al.* (2014); 103, Montano-Loza et al. (2016); 104, Wang *et al.* (2016); 105, Sebro (2017); 106, Coats *et al.*, (2018); 107, Bhanji *et al.* (2018); 108, Jahangiri *et al.* (2019); 109, Gioia *et al.* (2019); 110, Nardelli *et al.* (2019); 111, Mayer *et al.* (1989); 112, Ricq and Laroche, (2000); 113, Laroche and Cintas, (2010); 114, Sebro, O'Brien, Torriani, and Bredella (2016); 115, Azuma *et al.* (2017); 116, Kalichman, Klindukhov, Li, and Linov (2016); 117, Chang *et al.* (2018).

is convenient and easily accessed in health services (Heymsfield, et al., 1997; Daly, Prado, et al., 2018; Hopkins & Sawyer, 2018). DXA and MRI, instead, deliver little-to-no radiation when compared to CT, but are less available in the clinical setting, which hinders their use in clinical research (Lee, Shin, et al., 2019).

3.2 | Approaches to SM radiodensity assessment

A trend towards selecting L3 vertebrae and all abdominal region muscle was observed (Table 2). In contrast, there was a lack of standard in features that could significantly alter SM classification as high- or low-quality definitions, such as the contrast agents use (Table 2), selection of SM areas, radiodensity ranges delimitation and the cut-off points for these ranges (Table 3), as reported in previous reviews (Aubrey *et al.*, 2014; Kazemi-Bajestani *et al.*, 2016).

3.2.1 | Contrast agents use

Most studies (66.7%) (Table 2) did not mention the use of CT contrast agents. Rollins *et al.* (2017) showed that, among SMI, fat mass and fat-free mass body composition parameters, the average SM radiodensity was the one significantly affected by contrast application.

Contrast administration determines a highly positive radiodensity and radiation absorption in soft tissues and vessels, consequently allowing better visualization of the body structures. Thus, contrast increases the absorption of radiation in SM, which results in an increase of its radiodensity. In parallel, contrast use may lead to lower estimates of adipose tissue. Thereby, the effects of these agents on increasing SM radiodensity may be only partial in CT scans containing adipose tissue (Rollins *et al.*, 2017). Despite the observations concerning the impact of the contrast administration when assessing SM radiodensity, the literature in this area is still scarce and needs to be further studied (Rollins *et al.*, 2017; van der Werf *et al.*, 2018).

TABLE 2 Summarization of the methodologies used to evaluate the abdominal region and muscle groups by computed tomography

Evaluated points		% (*n*)	References
Contrast agents use	Not informed	66.7% (*n* = 78)	1; 2; 3; 4; 5; 6; 7; 8; 9; 10; 11; 12; 13; 14; 15; 16; 17; 18; 19; 20; 21; 22; 23; 24; 25; 26; 27; 28; 29; 30; 31; 32; 33; 34; 35; 36; 37; 38; 39; 40; 41; 42; 43; 44; 45; 46; 47; 48; 49; 50; 51; 52; 53; 54; 55; 56; 57; 58; 59; 60; 61; 62; 63; 64; 65; 66; 67; 68; 69; 70; 71; 72; 73; 74; 75; 76; 77; 78
	Contrast CT scans	17% (*n* = 20)	79; 80; 81; 82; 83; 84; 85; 86. 87; 88; 89; 90; 91; 92; 93; 94; 95; 96; 97; 98
	Non-contrast CT scans	11.1% (*n* = 13)	99; 100; 101; 102; 103; 104; 105; 106; 107; 108; 109; 110; 111
	Both contrast and non-contrast CT scans	5.2% (*n* = 6)	112; 113; 114; 115; 116; 117
Abdominal region	L3	76% (*n* = 89)	1; 6; 7; 9; 14; 15; 16; 17; 18; 19; 20; 21; 22; 23; 24; 25; 26; 27; 29; 32; 33; 34; 35; 36; 37; 38; 39; 40; 41; 42; 43; 44; 45; 46; 47; 48; 51; 52; 53; 54; 55; 57; 58; 60; 61; 62; 63; 64; 65; 66; 67; 68; 69; 70; 72; 73; 74; 75; 76; 77; 79; 81; 82; 83; 84; 85; 86; 87; 88; 89; 90; 91; 92; 93; 94; 95; 96; 97; 98; 103; 106; 107; 110; 111; 112; 113; 114; 115; 116
	L4 and L5	8.5% (*n* = 10)	2; 3; 4; 10; 30; 49; 50; 56; 59; 100
	L3, L4 and L5	4.3% (*n* = 5)	8; 99; 101; 102; 104
	L3 and L4	3.4% (*n* = 4)	31; 71; 80; 117
	Mid-abdominal level	2.6% (*n* = 3)	11; 12; 13
	L4	2.6% (*n* = 3)	105; 108; 109
	Umbilical level	1.7% (*n* = 2)	5; 28
	L3 and L5	0.85% (*n* = 1)	78
Muscle groups	Paraspinal muscles	7.7% (*n* = 9)	5; 6; 11; 12; 13; 78; 99; 100; 108
	Paraspinal and psoas muscles	4.3% (*n* = 5)	2; 31; 51; 105; 117
	Paraspinal and abdominal (rectus and lateral) muscles	1.7% (*n* = 2)	3; 4
	Paraspinal, psoas, internal and external obliques and rectus abdominus muscles	1.7% (*n* = 2)	1; 59
	Paraspinal, psoas, internal and external obliques, rectus abdominus, transversus spinae and latissimus dorsi muscles	0.85% (*n* = 1)	7
	Paraspinal, psoas, transversus abdominis, internal and external obliques, rectus abdominus and gluteus maximus muscles	0.85% (*n* = 1)	104
	Erector spinae, psoas, quadratus lumborum, transversus abdominis, internal and external obliques and rectus abdominus muscles	0.85% (*n* = 1)	110
	The dorsal portion of the muscles	0.85% (*n* = 1)	57

Abbreviations: L3, third lumbar vertebrae; L4, fourth lumbar vertebrae; L5, fifth lumbar vertebrae.

1, Mayer *et al.* (1989); 2, Goodpaster, Kelley, et al. (2000); 3, Hicks *et al.* (2005a); 4, Hicks *et al.* (2005b); 5, Komiya *et al.* (2006); 6, Laroche and Cintas (2010); 7, Anderson *et al.* (2013); 8, Anderson *et al.* (2014); 9, Antoun *et al.* (2013); 10, Miljkovic *et al.* (2013); 11, Therkelsen *et al.* (2013); 12, Therkelsen *et al.* (2016); 13, Kim *et al.* (2014); 14, Akahori *et al.* (2015); 15, Aust *et al.* (2015); 16, Malietzis *et al.* (2015); 17, Malietzis, Currie, et al. (2016); 18, Malietzis, Johns, et al. (2016); 19, Malietzis, Lee, et al. (2016); 20, Cushen *et al.* (2016); 21, Hayashi *et al.* (2016); 22, Kumar *et al.* (2016); 23, Looijaard *et al.* (2016); 24, Montano-Loza et al. (2016); 25, Rollins *et al.* (2016); 26, Wang *et al.* (2016); 27, Atlan *et al.* (2017); 28, Azuma *et al.* (2017); 29, Bye *et al.* (2017); 30, Erlandson *et al.* (2017); 31, Locke *et al.* (2017); 32, Loumaye *et al.* (2017); 33, Okumura *et al.* (2017b); 34, Rier *et al.* (2017); 35, Rier *et al.* (2018); 36, Shachar, Deal, Weinberg, Williams, et al. (2017); 37, Shachar, Deal, Weinberg, Nyrop, et al. (2017); 38, van Roekel *et al.* (2017); 39, Williams *et al.* (2017); 40, Williams *et al.* (2018); 41, Choi *et al.* (2018); 42, Rodrigues and Chaves, (2018); 43, Silva de Paula *et al.* (2018); 44, Souza *et al.* (2018); 45, Versteeg *et al.* (2018); 46, Charette *et al.* (2019); 47, Kiss et al. (2019); 48, Zhang *et al.* (2018); 49, Coats *et al.* (2018); 50, Vella *et al.* (2018); 51, Dohzono *et al.* (2019); 52, van Baar *et al.* (2018); 53, Atasevenet et al. (2018); 54, Bhanji *et al.* (2018); 55, Stretch *et al.* (2018); 56, Maltais *et al.* (2018); 57, van Dijk *et al.* (2018); 58, van Vugt, Gaspersz, et al. (2019); 59, van Hollebeke *et al.* (2018); 60, Silva de Paula *et al.* (2019); 61, Weinberg *et al.* (2018); 62, Sheean *et al.* (2019); 63, Sueda *et al.* (2018); 64, Bhanji, Narayanan, et al. (2019); 65, Bhanji, Takahashi, et al. (2019); 66, Caan *et al.* (2018); 67, Cortellini *et al.* (2018); 68, da Rocha *et al.* (2019); 69, Dolan *et al.* (2019); 70, Dusseaux *et al.* (2019); 71, Gioia *et al.* (2019); 72, Grønberg *et al.* (2019); 73, Lin *et al.* (2019); 74, Nardelli *et al.* (2019); 75, van der Kroft *et al.* (2018); 76, Xiao *et al.* (2019); 77, Xiao *et al.* (2018); 78, Ricq and Laroche (2000); 79, Fujiwara *et al.* (2015); 80, Boer *et al.* (2016); 81, Pędziwiatr *et al.* (2016); 82, Sjøblom *et al.* (2016); 83, Tamandl *et al.* (2016); 84, Daly *et al.* (2017); 85, Daly, Ní Bhuachalla, et al. (2018); 86, van Grinsven *et al.* (2017); 87, Van Rijssen *et al.* (2017); 88, Ní Bhuachalla *et al.* (2018); 89, Martin *et al.* (2018); 90, van Vugt *et al.* (2018); 91, van der Werf *et al.* (2018); 92, Brown *et al.* (2018); 93, Chakedis *et al.* (2018); 94, Dijksterhuis *et al.* (2019); 95, Lee, Lin, et al. (2019); 96, McSorley *et al.* (2018); 97, Tachi, Kozuka, Hirai, Kojima, et al. (2018); 98, van Vugt, van Putten, et al. (2019); 99, Kalichman *et al.* (2010); 100, Kalichman *et al.* (2016); 101, Sebro *et al.* (2016); 102, Idoate *et al.* (2017); 103, Okumura *et al.* (2017a), 104, Sebro (2017); 105, Deng *et al.* (2018); 106, Matsumoto *et al.* (2018); 107, Graffy *et al.* (2019); 108, Chang *et al.* (2018); 109, Jahangiri *et al.* (2019); 110, Lenchik *et al.* (2019); 111, Tachi, Kozuka, Hirai, Ishizu, et al. (2018); 112, Martin *et al.* (2013); 113, Chu *et al.* (2017); 114, Kubo *et al.* (2017); 115, Kroenke *et al.* (2018); 116, Hong *et al.* (2019); 117, Linder *et al.* (2019).

TABLE 3 Summarization of the methodologies used for skeletal muscle radiodensity classification by computed tomography

Evaluated points		% (*n*)	References
SM areas selection	Mean radiodensity of the total abdominal muscles area	79.5% (*n* = 93)	1; 2; 3; 4; 5; 6; 7; 8; 9; 10; 11; 12; 13; 14; 15; 16; 17; 18; 19; 20; 21; 22; 23; 24; 25; 26; 27; 28; 29; 30; 31; 32; 33; 34; 35; 36; 37; 38; 39; 40; 41; 42; 43; 44; 45; 46; 47; 48; 49; 50; 51; 52; 53; 54; 55; 56; 57; 58; 59; 60; 61; 62; 63; 64; 65; 66; 67; 68; 69; 70; 71; 72; 73; 74; 75; 76; 77; 78; 79; 80; 81; 82; 83; 84; 85; 86; 87; 88; 89; 90; 91; 92; 93
	Regions of interest	11.1% (*n* = 13)	94; 95; 96; 97; 98; 99; 100; 101; 102; 103; 104; 105; 106
	Mean radiodensity of the total abdominal muscles area and skeletal muscle gauge	6% (*n* = 7)	107; 108; 109; 110; 111; 112; 113
	High- or low-radiodensity SM indexes area	2.6% (*n* = 3)	92; 114; 115
	High- or low-radiodensity SM area	0.85% (*n* = 1)	116
	Did not inform the methodology used for this topic	0.85% (*n* = 1)	117
Radiodensity ranges	SM: −29HU to + 150HU	43.6% (*n* = 51)	12; 13; 14; 15; 16; 17; 19; 20; 21; 29; 32; 33; 34; 36; 38; 39; 40; 41; 43; 46; 47; 52; 54; 55; 57; 59; 60; 62; 68; 69; 73; 75; 76; 78; 79; 80; 81; 82; 83; 86; 87; 88; 103; 104; 106; 107; 108; 109; 110; 111; 113
	Did not inform the methodology used for this topic	17.9% (*n* = 21)	1; 3; 4; 5; 6; 9; 18; 30; 48; 51; 64; 66; 67; 74; 77; 94; 95; 99; 101; 105; 117
	SM: −29HU to + 150HU; intermuscular fat: −190HU to −30HU	9.4% (*n* = 11)	23; 24; 25; 45; 50; 58; 61; 85; 90; 91; 112
	SM: −29HU to + 150HU; intramuscular fat: −190HU to −30HU	6% (*n* = 7)	22; 26; 27; 28; 31; 44; 49
	SM: −30HU to + 150HU	6% (*n* = 7)	65; 70; 71; 72; 84; 89; 102
	Fat range (general)	2.6% (*n* = 3)	96; 97; 98
	SM: 0HU to + 100HU	2.6% (*n* = 3)	2; 93; 100
	SM: −50HU to + 150HU	1.7% (*n* = 2)	7; 8
	Low-radiodensity SM: −29HU to + 29HU; high-radiodensity SM: +30HU to + 150HU	1.7% (*n* = 2)	92; 115
Radiodensity ranges	Low-radiodensity SM: −29HU to + 29HU; high-radiodensity SM: +30HU to + 150HU; intramuscular fat: −190HU to −30HU	0.85% (*n* = 1)	114
	SM: 0HU to + 100HU; intermuscular fat: −190HU to −30HU	0.85% (*n* = 1)	11
	SM: −29HU to + 150HU; low SM radiodensity: −29HU to + 29 HU	0.85% (*n* = 1)	10
	SM: −29HU to + 160HU	0.85% (*n* = 1)	37
	Intermuscular fat: ≤30HU	0.85% (*n* = 1)	35
	SM: −29HU to + 150HU; intramuscular fat: −190HU to −90HU	0.85% (*n* = 1)	42
	SM: 0HU to + 100 HU, considering low-radiodensity SM: 0HU to + 29HU and high-radiodensity SM: +30HU to + 100HU	0.85% (*n* = 1)	116
	SM: −19HU to + 150HU	0.85% (*n* = 1)	53
	Residual SM: −29HU to −1 HU; low-radiodensity SM: 0HU to + 34HU; normal radiodensity SM: +35HU to + 100 HU; mean radiodensity SM: −29HU to + 100 HU	0.85% (*n* = 1)	63
	SM: 0HU to + 100HU; undefined tissue type: −30HU to 0HU	0.85% (*n* = 1)	56

(Continues)

TABLE 3 (Continued)

Evaluated points		% (*n*)	References
Cut-off points	Cut-off points established for the evaluated population, through statistical analyses, tercile and quartile	33.3% (*n* = 39)	10; 11; 12; 13; 14; 27; 28; 31; 39; 40; 43; 44; 46; 52; 55; 57; 58; 59; 60; 63; 64; 65; 67; 73; 74; 86; 90; 91; 92; 93; 96; 97; 99, 102; 112; 113; 114; 115; 116
	Cut-off points not established: SM radiodensity analysed as a continuous variable and mean and median values of the entire abdominal region were compared among groups	29% (*n* = 34)	1; 2; 3; 4; 5; 6; 7; 9; 19; 22; 23; 30; 35; 36; 37; 42; 47; 49; 51; 68; 75; 79; 80; 81; 82; 83; 94; 98; 100; 105; 107; 108; 109; 110
	Cut-off points pre-established by Martin *et al.* (2013)	27.3% (*n* = 32)	15; 17; 18; 20; 21; 24; 25; 26; 29; 32; 33; 34; 41; 48; 50; 53; 61; 65; 66; 69; 70; 71; 72; 77; 78; 84; 85; 87; 89; 104; 106; 111
	Mean of the entire abdominal region continuously, correlation tests and linear regression	3.4% (*n* = 4)	8; 56; 62; 93; 103
Cut-off points	Cut-off point < 30HU (Aubrey *et al.*, 2014; Goodpaster, Kelley, et al., 2000)	1.7% (*n* = 2)	38; 62
	Cut-off points pre-established for visceral, subcutaneous and total fat (Doyle *et al.*, 2013) and sarcopenia (the study showed only the mean SM radiodensity for its population) (Prado *et al.*, 2008)	0.85% (*n* = 1)	16
	Values of each muscle group alone as continuous variables	0.85% (*n* = 1)	101
	Mean of the continuous variable of all groups and terciles did not stratified by sex	0.85% (*n* = 1)	45
	Mean of the continuous variable of all groups and cut-off points created for a MQ Index: RDR = Radiographic Muscle Density/Standard Deviation of Density	0.85% (*n* = 1)	95
	Cut-off points established for the evaluated population, through median	0.85% (*n* = 1)	88
	Cut-off points pre-established by Sjøblom *et al.* (2016)	0.85% (*n* = 1)	76
	Cut-off points pre-established by Xiao *et al.* (2018)	0.85% (*n* = 1)	104
	Cut-off points pre-established by Fujiwara *et al.* (2015)	0.85% (*n* = 1)	54
	Did not inform the methodology used for this topic	0.85% (*n* = 1)	117

Abbreviations: HU, Hounsfield units; MQ, muscle quality; RDR, radiographic density ratio; SM, skeletal muscle.

1, Mayer *et al.* (1989); 2, Goodpaster, Kelley, et al. (2000); 3, Ricq and Laroche, (2000); 4, Hicks *et al.* (2005a); 5, Hicks *et al.* (2005b); 6, Komiya *et al.* (2006); 7, Anderson *et al.* (2013); 8, Anderson *et al.* (2014); 9, Antoun *et al.* (2013); 10, Martin *et al.* (2013); 11, Miljkovic *et al.* (2013); 12, Akahori *et al.* (2015); 13, Aust *et al.* (2015); 14, Fujiwara *et al.* (2015); 15, Malietzis *et al.* (2015); 16, Malietzis, Currie, et al. (2016); 17, Malietzis, Johns, et al. (2016); 18, Malietzis, Lee, et al. (2016); 19, Boer *et al.* (2016); 20, Cushen *et al.* (2016); 21, Hayashi *et al.* (2016); 22, Kumar *et al.* (2016); 23, Looijaard *et al.* (2016); 24, Montano-Loza et al. (2016); 25, Pędziwiatr *et al.* (2016); 26, Rollins *et al.* (2016); 27, Sjøblom *et al.* (2016); 28, Tamandl *et al.* (2016); 29, Wang *et al.* (2016); 30, Atlan *et al.* (2017); 31, Bye *et al.*; (2017); 32, Chu *et al.* (2017); 33, Daly *et al.* (2017); 34, Daly, Ní Bhuachalla, et al. (2018); 35, Erlandson *et al.* (2017); 36, Kubo *et al.* (2017); 37, Locke *et al.* (2017); 38, Loumaye *et al.* (2017); 39, Okumura *et al.* (2017a); 40, Okumura *et al.* (2017b); 41, Rier *et al.* (2017); 42, Rier *et al.* (2018); 43, van Grinsven *et al.* (2017); 44, Van Rijssen *et al.* (2017); 45, van Roekel *et al.* (2017); 46, Choi *et al.* (2018); 47, Matsumoto *et al.* (2018); 48, Ní Bhuachalla *et al.* (2018); 49, Souza *et al.* (2018); 50, Versteeg *et al.* (2018); 51, Graffy *et al.* (2019); 52, Charette *et al.* (2019); 53, Kiss et al. (2019); 54, Zhang *et al.* (2018); 55, Coats *et al.* (2018); 56, Vella *et al.* (2018); 57, Dohzono *et al.* (2019); 58, van Baar *et al.* (2018); 59, Atasevenet et al. (2018; 60, Martin *et al.* (2018); 61, Bhanji *et al.* (2018); 62, Stretch *et al.* (2018); 63, Maltais *et al.* (2018); 64, van Dijk *et al.* (2018); 65, van Vugt, Gaspersz, et al. (2019); 66, van Vugt *et al.* (2018); 67, Kroenke *et al.* (2018); 68, van der Werf *et al.* (2018); 69, Sheean *et al.* (2019); 70, Sueda *et al.* (2018); 71, Bhanji, Narayanan, et al. (2019); 72, Bhanji, Takahashi, et al. (2019); 73, Brown *et al.* (2018); 74, Caan *et al.* (2018); 75, Chakedis *et al.* (2018); 76, Cortellini *et al.* (2018); 77, da Rocha *et al.* (2019); 78, Dijksterhuis *et al.* (2019); 79, Dusseaux *et al.* (2019); 80, Gioia *et al.* (2019); 81, Grønberg *et al.* (2019); 82, Hong *et al.* (2019); 83, Lenchik *et al.* (2019); 84, Linder *et al.* (2019); 85, Nardelli *et al.* (2019); 86, Tachi, Kozuka, Hirai, Ishizu, et al. (2018); 87, Tachi, Kozuka, Hirai, Kojima, et al. (2018); 88, van der Kroft *et al.* (2018); 89, van Vugt, van Putten, et al. (2019); 90, Xiao *et al.* (2019); 91, Xiao *et al.* (2018); 92, Silva de Paula *et al.* (2019); 93, van Hollebeke *et al.* (2018); 94, Kalichman *et al.* (2010); 95, Kalichman *et al.* (2016); 96, Therkelsen *et al.* (2013); 97, Therkelsen *et al.* (2016), 98, Kim *et al.* (2014); 99, Sebro *et al.* (2016); 100, Azuma *et al.* (2017); 101, Sebro (2017); 102, Deng *et al.* (2018); 103, Chang *et al.* (2018); 104, Dolan *et al.* (2019); 105, Jahangiri *et al.* (2019); 106, McSorley *et al.* (2018); 107, Shachar, Deal, Weinberg, Williams, et al. (2017); 108, Shachar, Deal, Weinberg, Nyrop, et al. (2017); 109, Williams *et al.* (2017); 110, Williams *et al.* (2018); 111, Weinberg *et al.* (2018); 112, Lee, Lin, et al. (2019); 113, Lin *et al.* (2019); 114, Rodrigues and Chaves, (2018); 115, Silva de Paula *et al.* (2018); 116, Idoate *et al.* (2017); 117, Laroche and Cintas (2010).

TABLE 4 Summarization of the terms used to evaluate and refer to skeletal muscle radiodensity by computed tomography

Used terms	% (*n*)	References
SM attenuation/MA	53.8% (*n* = 63)	2; 4; 5; 6; 7; 8; 10; 12; 14; 15; 16; 17; 18; 20; 22; 23; 24; 28; 29; 33; 34; 36; 37; 39; 40; 41; 42; 43; 44; 45; 49; 50; 52; 53; 54; 55; 59; 61; 63; 66; 70; 71; 72; 77; 80; 83; 84; 85; 86; 87; 88; 92; 96; 97; 98; 100; 102; 105; 108; 109; 110; 114; 116
SM density/Muscle density	41% (*n* = 48)	1; 3; 9; 21; 22; 23; 30; 32; 35; 38; 42; 43; 46; 47; 48; 51; 53; 56; 57; 58; 65; 66; 67; 68; 69; 74; 75; 78; 79; 81; 84; 86; 87; 88; 89; 93; 94; 95; 99; 101; 103; 105; 107; 108; 109; 110; 111; 116
SM radiodensity/Muscle radiodensity/ Radiological SM attenuation	30.8% (*n* = 36)	9; 13; 20; 23; 25; 26; 27; 30; 31; 32; 38; 45; 46; 48; 50; 57; 60; 62; 64; 68; 69; 73; 74; 76; 79; 82; 88; 90; 91; 92; 104; 106; 111; 112; 114; 115
Myosteatosis	22.2% (*n* = 26)	4; 15; 16; 18; 19; 24; 26; 29; 42; 54; 61; 62; 64; 69; 70; 71; 72; 85; 86; 92; 95; 104; 106; 111; 114; 116
Intramuscular AT/Intramuscular fat	16.2% (*n* = 19)	6; 14; 22; 26; 27; 28; 39; 42; 43; 44; 48; 49; 67; 74; 89; 96; 97; 98; 114
SM quality/MQ	14.5% (*n* = 17)	14; 19; 23; 29; 36; 39; 40; 43; 69; 74; 76; 95; 100; 110; 113; 115; 116;
Muscle fat infiltration	11.1% (*n* = 13)	4; 5; 20; 24; 29; 42; 45; 47; 71; 80; 85; 95; 116
Muscle fat content/Muscle lipid content/Lipid in muscle/Triglyceride muscle content	10.2% (*n* = 12)	9; 21; 36; 49; 73; 79; 96; 97; 100; 108; 109; 110
Intermuscular AT	7.7% (*n* = 9)	2; 5; 11; 23; 24; 45; 50; 90; 91
Fatty muscle infiltration	6.8% (*n* = 8)	9; 13; 19; 30; 35; 69; 79; 117
Intermuscular fat	2.6% (*n* = 3)	22; 35; 48
Muscle composition	1.7% (*n* = 2)	4; 5
Intramyocellular triglycerides	1.7% (*n* = 2)	114; 115
Fat deposits	0.85% (*n* = 1)	94
Muscle lipid infiltration	0.85% (*n* = 1)	23
Sarcopenia (considering area and MA)	0.95% (*n* = 1)	110

Abbreviations: AT, adipose tissue; MA, muscle attenuation; MQ, muscle quality; SM, skeletal muscle.

1, Mayer *et al.* (1989); 2, Goodpaster, Kelley, et al. (2000); 3, Ricq and Laroche, (2000); 4, Hicks *et al.* (2005a); 5, Hicks *et al.* (2005b); 6, Komiya *et al.* (2006); 7, Anderson *et al.* (2013); 8, Anderson *et al.* (2014); 9, Antoun *et al.* (2013); 10, Martin *et al.* (2013); 11, Miljkovic *et al.* (2013); 12, Akahori *et al.* (2015); 13, Aust *et al.* (2015); 14, Fujiwara *et al.* (2015); 15, Malietzis *et al.* (2015); 16, Malietzis, Currie, et al. (2016); 17, Malietzis, Johns, et al. (2016); 18, Malietzis, Lee, et al. (2016); 19, Boer *et al.* (2016); 20, Cushen *et al.* (2016); 21, Hayashi *et al.* (2016); 22, Kumar *et al.* (2016); 23, Looijaard *et al.* (2016); 24, Montano-Loza et al. (2016); 25, Pędziwiatr *et al.* (2016); 26, Rollins *et al.* (2016); 27, Sjøblom *et al.* (2016); 28, Tamandl *et al.* (2016); 29, Wang *et al.* (2016); 30, Atlan *et al.* (2017); 31, Bye *et al.* (2017); 32, Chu *et al.* (2017); 33, Daly *et al.* (2017); 34, Daly, Ní Bhuachalla, et al. (2018); 35, Erlandson *et al.* (2017); 36, Kubo *et al.* (2017); 37, Locke *et al.* (2017); 38, Loumaye *et al.* (2017); 39, Okumura *et al.* (2017a); 40, Okumura *et al.* (2017b); 41, Rier *et al.* (2017); 42, Rier *et al.* (2018); 43, van Grinsven *et al.* (2017); 44, Van Rijssen *et al.* (2017); 45, van Roekel *et al.* (2017); 46, Choi *et al.* (2018); 47, Matsumoto *et al.* (2018). 48, Ní Bhuachalla *et al.* (2018); 49, Souza *et al.* (2018); 50, Versteeg *et al.* (2018); 51, Graffy *et al.* (2019); 52, Charette *et al.* (2019); 53, Kiss et al. (2019); 54, Zhang *et al.* (2018); 55, Coats *et al.* (2018); 56, Vella *et al.* (2018); 57, Dohzono *et al.* (2019); 58, van Baar *et al.* (2018); 59, Atasevenet et al. (2018); 60, Martin *et al.* (2018); 61, Bhanji *et al.* (2018); 62, Stretch *et al.* (2018); 63, Maltais *et al.* (2018); 64, van Dijk *et al.* (2018); 65, van Vugt, Gaspersz, et al. (2019); 66, van Vugt *et al.* (2018); 67, Kroenke *et al.* (2018); 68, van der Werf *et al.* (2018); 69, Sheean *et al.* (2019); 70, Sueda *et al.* (2018); 71, Bhanji, Narayanan, et al. (2019); 72, Bhanji, Takahashi, et al. (2019); 73, Brown *et al.* (2018); 74, Caan *et al.* (2018); 75, Chakedis *et al.* (2018); 76, Cortellini *et al.* (2018); 77, da Rocha *et al.* (2019); 78, Dijksterhuis *et al.* (2019); 79, Dusseaux *et al.* (2019); 80, Gioia *et al.* (2019); 81, Grønberg *et al.* (2019); 82, Hong *et al.* (2019); 83, Lenchik *et al.* (2019); 84, Linder *et al.* (2019); 85, Nardelli *et al.* (2019); 86, Tachi, Kozuka, Hirai, Ishizu, et al. (2018); 87, Tachi, Kozuka, Hirai, Kojima, et al. (2018); 88, van der Kroft *et al.* (2018); 89, van Vugt, van Putten, et al. (2019); 90, Xiao *et al.* (2019); 91, Xiao *et al.* (2018); 92, Silva de Paula *et al.* (2019); 93, van Hollebeke *et al.* (2018); 94, Kalichman *et al.* (2010); 95, Kalichman *et al.* (2016); 96, Therkelsen *et al.* (2013); 97, Therkelsen *et al.* (2016), 98, Kim *et al.* (2014); 99, Sebro *et al.* (2016); 100, Azuma *et al.* (2017); 101, Sebro, (2017); 102, Deng *et al.* (2018); 103, Chang *et al.* (2018); 104, Dolan *et al.* (2019); 105, Jahangiri *et al.* (2019); 106, McSorley *et al.* (2018); 107, Shachar, Deal, Weinberg, Williams, et al. (2017); 108, Shachar, Deal, Weinberg, Nyrop, et al. (2017); 109, Williams *et al.* (2017); 110, Williams *et al.* (2018); 111, Weinberg *et al.* (2018); 112, Lee, Lin, et al. (2019); 113, Lin *et al.* (2019); 114, Rodrigues and Chaves (2018); 115, Silva de Paula *et al.* (2018); 116, Idoate *et al.* (2017); 117, Laroche and Cintas (2010).

3.2.2 | Abdominal region

Similarly as reported in a previous review (Kazemi-Bajestani *et al.*, 2016), CT cross-sectional image at L3 level was the most frequent among the included articles (Table 2). The predominant use of this vertebral level is related to its linear correlation with total body skeletal muscle mass, demonstrated in a validation study (Shen *et al.*, 2004). Two references (Table 2) reported the use of images at the umbilical level, however, this is a non-static reference point, which could result in a measurement error (Hopkins *et al.*, 2018).

Although the CT abdominal region is the most frequently used point, there are also studies using peripheral CT for SM evaluation,

such as the mid-thigh image (Lee, Lin, *et al*., 2019). However, studies reporting peripheral CT approach both in healthy and diseased individuals also take advantage on the examination prescription for clinical diagnosis (i.e. vascular, musculoskeletal and others) (Cleary *et al*., 2015; Khoja, Patterson, Goodpaster, elitto, & Piva, 2020; Morris, Skalina, Singh, Moxon, & Golledge, 2018). Nevertheless, to date, it is still not possible to determine which region is the most promising and accurate option for SM quality characterization, withal the abdominal level probably represents the body muscle in a larger scale, while peripheral CT does not deliver high-dose radiation, besides being portable and easier to use. The availability of multiple protocols for SM assessment by image tools limits the method standardization and, in turn, its potential use in predicting clinical outcomes (Lee, Shin, et al., 2019).

3.2.3 | Muscle groups

The assessment of all muscle groups was observed in the majority (81.2%) of the studies (Table 2). Appraising the total cross-sectional muscle area is more sensitive to delimit total SM and has a stronger interobserver agreement (Rutten *et al*., 2017; van Dijk *et al*., 2017). Paraspinals (erector spinae—including iliocostalis, longissimus and multifidus—and quadratus lumborum), psoas and abdominal wall muscles (transversus abdominis, internal and external obliques, and rectus abdominus) are considered as components of the muscle set at the abdominal region (Daly, Prado, et al., 2018; Gomez-Perez *et al*., 2016; Hopkins & Sawyer, 2018).

On the other hand, the analysis of only one abdominal muscle group—as reported by two studies (Sabel *et al*., 2011; Yamashita *et al*., 2017)—is not recommended, since such methodology has not been validated and presents a significant bias risk. Appraising only *psoas* muscle as representative of the total abdominal muscle group, for instance, demonstrates a high measurement error, weak correlation with the total lumbar muscle area and is susceptible to atrophy due to diseases of the spine (Baracos, 2017; Hopkins & Sawyer, 2018; Hopkins *et al*., 2018; Rutten *et al*., 2017).

3.2.4 | Selection of the skeletal muscle groups areas for muscle radiodensity assessment

There was a predominance of studies using the average SM radiodensity of the total abdominal muscles area in the cross-sectional images. Other authors determined the muscle radiodensity using only a SM-specific region, usually denominated as "region of interest" (Table 3). However, such measure may be a bias, as it considers only one region as representative of the whole muscle groups, when, in fact, the muscle composition is heterogeneous between the different groups (Mourtzakis *et al*., 2008). Furthermore, small measurement errors of an isolated tissue portion could mathematically generate higher errors when this region is extrapolated to the total body skeletal muscle tissue (Rutten *et al*., 2017).

The use of a mathematical index generated by Weinberg *et al*. (2016), called "skeletal muscle gauge" (Table 3), that multiplies SM index (SM area multiplied by the square height) by mean muscle radiodensity was claimed by the authors as a superior measure since it integrates both SM quantity and quality (radiodensity) in the same variable. This new indicator showed a stronger correlation with age, in addition to a greater power to predict toxicity and hospitalizations in patients undergoing chemotherapy (Shachar, Deal, Weinberg, Nyrop, *et al*., 2017; Shachar, Deal, Weinberg, Williams, *et al*., 2017), when compared to the isolated indexes. However, it was not associated with overall survival in patients with metastatic breast cancer (Shachar, Deal, Weinberg, Nyrop, *et al*., 2017). The combined measure is presented in Arbitrary Units (AU) since the SM area and radiodensity hold different measure units (Weinberg *et al*., 2016, 2018).

Studies dividing total SM range into two subranges, denominated as "low- or high-radiodensity SM," were also found (Table 3). The researchers calculated the representative muscle area of these two ranges, alleging that this methodology allows the identification of the extent of SM area with presumed more or less fat infiltration, instead of only classifying it based on mean radiodensity (Silva de Paula *et al*., 2018).

3.2.5 | Radiodensity ranges

Regarding the radiodensity ranges for SM delimitation, we observed a trend towards standardization (Table 3), which corroborates previous reviews (Aubrey *et al*., 2014; Kazemi-Bajestani *et al*., 2016). We observed a predominance (43.6%) of the range from −29HU to + 150HU. Intervals from −50HU to + 150HU, −30HU to + 150HU, −29HU to + 160HU and from 0HU to + 100HU were also used (Table 3).

While for the low-radiodensity SM ranges, there was not found a pattern among authors. Some articles established as low-radiodensity the ranges from −29HU to + 29HU and from 0HU to + 29HU, while others used the interval from 0HU to + 34HU. Researchers in our group named the interval from −29HU to + 29HU as "low-radiodensity SM," while the interval from + 30HU to + 150HU was determined as "high-radiodensity SM." The range from + 30HU to + 100HU for high-radiodensity SM was also identified (Table 3).

Likewise, variations in the tissue range equal or lower than −30HU are also observed. However, the area below −30HU is already consolidated by the literature as fat per se and, when located within the muscle groups, is applied to estimate individuals' body fat (Mitsiopoulos *et al*., 1998).

Variations also included a radiodensity interval from −30HU to 0HU, called undefined tissue type, and a radiodensity range lower or equal to + 30HU, to discriminate intermuscular fat. An article not included in our results considered the range from −200HU to −1HU as solely fat (Kelley, Slasky, & Janosky, 1991).

Some articles have considered not only muscle tissue radiodensity, but also the range equal or lower than −30HU as a parameter for SM quality. Thus, some authors designate as intermuscular and

intramuscular fat the ranges covering tissues presenting radiodensity between −190HU and −30HU. The interval −190HU to −90HU was also named as intramuscular fat (Table 3). These terms define lipid infiltration both outside and inside the myocyte, respectively, but CT is not capable of differentiating it, as previously mentioned (Goodpaster, 2002).

This diversity in the radiodensity ranges used (Figure 2), mainly in relation to the lower point of what is considered as SM range, may be related to the difficulty in defining the tenuous point that differentiates the adiposity tissue of the low-radiodensity SM. Excluding the range from −29HU to 0HU to account for SM area implies that any region within this radiodensity range would be neither muscle nor adipose tissue. Thus, using the total range from −29HU to + 29HU to define low SM radiodensity (or myosteatosis) has been encouraged (Aubrey *et al*., 2014).

In 1979, even without full knowledge of how tissue biochemistry relates to muscle radiodensity, it was already supposed that the concentration of main contractile proteins and enzymes—myoglobin, haemoglobin, collagen—in addition to fat content was important factors to define muscle radiodensity (Bulcke, Termote, Palmers, & Crolla, 1979). In the following years, some authors have stated that portions of SM radiodensity range could also be consisted of other lean tissues, muscular components and connective tissue elements. However, it is still not clear what determines the lower muscle radiodensity (Kelley *et al*., 1991; Sjöström, 1991; Sjöström et al., 1993; Chowdhury *et al*., 1994; Chowdhury, Lantz, & Sjostrom, 1996; Heymsfield, Wang, Baumgartner, & Ross, 1997).

A validation study, comparing SM radiodensity to the triglyceride content in muscle biopsy (Goodpaster, Kelley, et al., 2000), suggested that this imaging method is capable of inferring SM fat content (Daly, Prado, et al., 2018; Goodpaster, Kelley, et al., 2000; Miljkovic & Zmuda, 2010). However, the same authors pointed that it would be unlikely that lipid content was the only contributor to the variations in muscle radiodensity. Other factors or changes in SM properties such as muscle protein, perfusion or extracellular water content could also affect it (Goodpaster, Kelley, et al., 2000; Goodpaster Thaete, & Kelley, 2000). Thus, the precise histological and biochemical knowledge of the tissues that compose the low-radiodensity SM range is still scarce. Currently, the most widely accepted molecular constituent likely to cause the marked reduction in SM radiodensity is the accumulated fat (Chabowski, Żendzian-Piotrowska, Nawrocki, & Górski, 2012). Nevertheless, other possible molecular contributions need to be considered in future studies.

CT methodological limitations, approach disagreements and the arbitrary selection of muscle radiodensity spectrum, result therefore in variations for the proposed nomenclatures, which will be discussed later. This scenario and even intervals omission can lead to failures in the evaluation of a significant and clinically representative skeletal muscle total area (Aubrey *et al*., 2014).

3.2.6 | Cut-off points

The majority of studies, especially the most recent ones, stipulated cut-off points for their own population. Thereby, another

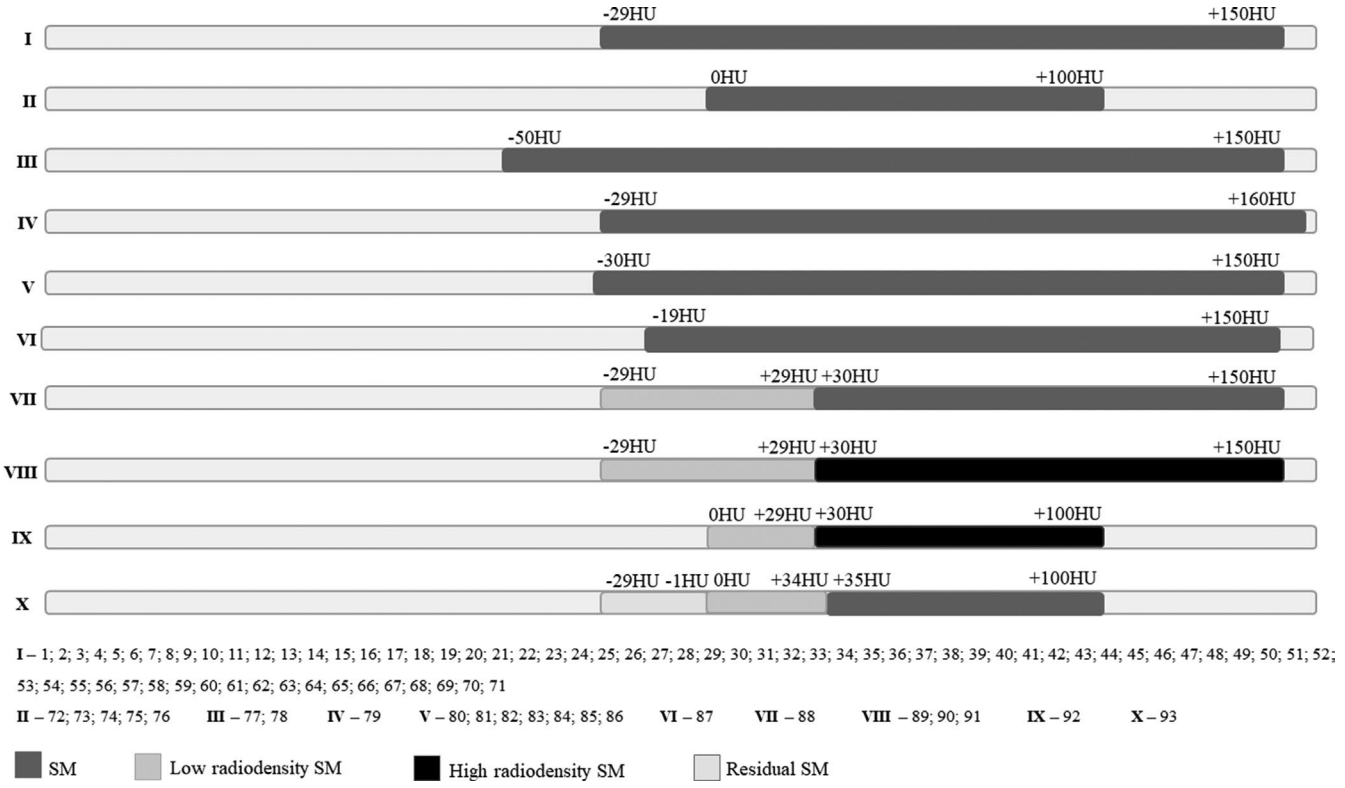

FIGURE 2 Ranges used to delimit SM areas according its CT-based radiodensity. HU, Hounsfield Units; SM, Skeletal Muscle

significant number of studies analysed their findings using the SM radiodensity as a continuous variable [representative tissue area of radiodensity, in cm^2/m^2, or mean radiodensity, in HU] for mean or median comparison with the dependent variables of interest, without establishing cut-off points for the radiodensity ranges used (Table 3).

More than 27% of the studies used as a parameter the set of cut-off points for low-radiodensity muscle determined by Martin *et al.* (2013) (using optimal stratification) in cancer patients (Daly, Prado, et al., 2018). Six articles used pre-established cut-off points from other studies (Aubrey *et al.*, 2014; Doyle *et al.*, 2013; Fujiwara *et al.*, 2015; Goodpaster, Kelley, et al., 2000; Prado *et al.*, 2008; Sjøblom *et al.*, 2016; Xiao *et al.*, 2018), among which, one evaluated visceral, subcutaneous and total fat (Doyle *et al.*, 2013) and the other assessed sarcopenia, reporting only the mean SM radiodensity for its population, stratified by the presence of sarcopenia (Prado *et al.*, 2008) (Table 3).

Since the low-radiodensity range and its cut-off points are not standardized nor adequately defined, inconsistencies at data collection and analysis are expected, making the comparison of results difficult (Hopkins *et al.*, 2018). The standardization process must consider specific characteristics of factors such as age, sex, ethnicity and diseases (Kazemi-Bajestani *et al.*, 2016).

3.2.7 | Terminology evolution

Another relevant point is the terminology inconsistency to designate SM radiodensity (Table 4), which is a consequence of the methodological problems previously discussed (Aubrey *et al.*, 2014; Chabowski *et al.*, 2012). Among the nomenclatures observed in the articles, the ones that stood out were those referring to SM, such as "attenuation or radiological attenuation, radiodensity and density."

However, the use of "muscle attenuation" as a synonym for terms such as "SM radiodensity or density" needs to be better employed. According to Oxford and Cambridge Dictionaries (2019), respectively, "attenuation" means reducing the force, effect, or value of something, and "attenuating" means making something smaller, thinner or weaker. Its use in the context of SM quality seems to emerge from the fact that, when analysed by CT, the presence of fat attenuates SM radiodensity, because, as previously stated, this tool reads tissue radiodensity, generated by its chemical composition (Goodpaster, Kelley, et al., 2000). Thus, we reinforce that the term "SM radiodensity" is the most appropriate to be applied, considering the perspectives of interpretation presented here. In addition, it is not possible to accurately state what tissue is present, in the absence of a direct measure, since CT is an indirect measure of tissue composition (Goodpaster, Kelley, et al., 2000).

Terms referring to adipose tissue in muscles were found in a smaller amount of papers (Table 4), just as others more specific when designating the fat location in muscle, such as "intramuscular or intramyocellular" and "intermuscular." The presence of two cellular pathways of fat origin in SM enables these nomenclatures variations. The first pathway is direct and is due to lipid accumulation within the myocytes (Rivas *et al.*, 2016), whereas "intermuscular" variation is due to the accumulation of satellite cells (stem cell population) and mesenchymal interstitial cells below the basal lamina of muscle fibres (Dong, Silva, Dong, & Zhang, 2014; Farup, Madaro, Puri, & Mikkelsen, 2015; Hamrick, McGee-Lawrence, & Frechette, 2016). The first ones contribute to myogenesis during muscle regeneration and are more resistant to adipogenic differentiation, while the others differ rapidly in fat under muscle injury or glucocorticoids administration (Agley, Rowlerson, Velloso, Lazarus, & Harridge, 2013; Dong *et al.*, 2014; Hamrick *et al.*, 2016). Despite the broad possibility of extrapolating the SM radiodensity measurement as a predictor of SM fat content, it is imperative that readers and researchers interpret the results with caution, staying aware that CT provide an indirect measure (Table 4).

Fat infiltration in the SM is related to impaired energetic homeostasis, insulin insensitivity, inflammation and functional muscular deficits (Arsenault, Beaumont, Després, & Larose, 2012; Hamrick *et al.*, 2016), generating "SM quality or muscular quality" nominal variations (Table 4), due to tissue damage. Individuals presenting concomitantly insulin resistance and obesity may present a vicious cycle promoting SM fat accumulation, since both conditions can impair local fatty acids metabolism (Almasud *et al.*, 2017; Hamrick *et al.*, 2016; Penton, Thomas-Ahner, Johnson, McAllister, & Montanaro, 2013). Therefore, considering the important metabolic derangement attributable to SM fat infiltration, a robust methodology adjustment could enable the future application of CT-based SM radiodensity as a prognostic tool.

4 | CONCLUSION

This review indicates a trend towards standardization in using the abdominal region and all the muscle groups available in such region for SM radiodensity evaluation, while topics such as the contrast agents use, selection of SM areas, radiodensity ranges delimitation and their cut-off points were represented by multiple divergences, as well as the terms used for its nomenclature.

Continuing to use L3 and evaluating all muscle groups at this vertebral level is highly recommended, as well as the preference for total muscle area selection. Methodology definition to classify fat-infiltrated muscle tissue, according to its radiodensity, should be preferably validated with studies comparing CT radiological findings and direct methods of muscle composition assessment. It is also recommended to consider specificities of each studied population, which may impact radiodensity cut-off points. Nomenclature uniformization will benefit from the elucidation of these topics.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest associated with this manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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