Implications of low muscle mass across the continuum of care: a narrative review

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ABSTRACT
Abnormalities in body composition can occur at any body weight. Low muscle mass is a predictor of poor morbidity and mortality and occurs in several populations. This narrative review provides an overview of the importance of low muscle mass on health outcomes for patients in inpatient, outpatient and long-term care clinical settings. A one-year glimpse at publications that showcases the rapidly growing research of body composition in clinical settings is included. Low muscle mass is associated with outcomes such as higher surgical and post-operative complications, longer length of hospital stay, lower physical function, poorer quality of life and shorter survival. As such, the potential clinical benefits of preventing and reversing this condition are likely to impact patient outcomes and resource utilization/health care costs. Clinically viable tools to measure body composition are needed for routine screening and intervention. Future research studies should elucidate the effectiveness of multimodal interventions to counteract low muscle mass for optimal patient outcomes across the healthcare continuum.

KEY MESSAGES
- Low muscle mass is associated with several negative outcomes across the healthcare continuum.
- Techniques to identify and counteract low muscle mass in clinical settings are needed.

Introduction

Measures of body mass such as weight and body mass index (BMI) have long been regarded as practical and sensitive for the prediction of health risks and outcomes. Although of value, these measurements do not depict an individual’s variability in body composition (i.e. lean versus adipose tissue). Body composition can be variable among individuals of the same body size, confounding the association between body weight and health, Figure 1(a,b). Abnormalities in body composition such as low muscle mass are powerful predictors of morbidity and mortality, particularly in clinical settings where the disease or illness itself can lead to this condition [1,2]. In this narrative review, we provide an overview of the importance of low muscle mass on health outcomes for patients in inpatient, outpatient and long-term care clinical settings, as well as a past year review of the literature.

Low muscle mass: a new face of an old problem

From a theoretical standpoint, skeletal muscle is a primary driver of the relationship between body composition and clinical outcomes, as it is involved in mobility, strength and balance. However, there are several methods to measure body composition and as a result, there are many constructs and terms that
Figure 1. Body composition across the body weight continuum. Low muscle mass can occur in people with obesity (1a) and at any body weight (1b) BMI: body mass index.

Table 1. Commonly used terminology in body composition research.

| Terminology               | Description                                                                 | Technique          |
|---------------------------|-----------------------------------------------------------------------------|--------------------|
| Fat-free mass             | Sum of skeletal and non-skeletal muscle, organs, connective tissue and bone  | DXA, ADP, BIAa      |
| Lean soft tissue or lean mass b | Sum of all lean tissues includes protein, water, carbohydrates, non-fat lipids, soft tissue minerals (excludes bone and fat) | DXA               |
| Skeletal muscle mass      | The total mass of skeletal muscle                                           | US, MRI, CT        |
| Appendicular skeletal muscle mass | Lean soft tissue (or lean mass) from arms and legs which is skeletal muscle (except from a negligible amount of skin). | DXA               |
| Muscle radiodensity or attenuation | Reflective of intermuscular adipose tissue or ‘quality’ of skeletal muscle; low muscle radiodensity/attenuation are reflective of higher amount of fat infiltration | CT, MRI          |
| Sarcopenia                | Low muscle mass in combination with low strength, muscular performance, or physical performance | Several techniques are availablec |

aBIA estimates this compartment (versus direct measurement). Additionally, equations can be used to estimate skeletal muscle from BIA measurements.

bThe term lean body mass is not specific and should no longer be used.

cConsensus definitions of sarcopenia have employed several methods, although the accuracy of these techniques varies. ADP: air displacement plethysmography; BIA: bioelectrical impedance analysis; CT: computerized tomography; DXA: dual X-ray absorptiometry; MRI: magnetic resonance imaging; US: ultrasound.
ultimately reflect this compartment in the research hereby discussed (Table 1). Therefore, for clarity, we will refer to “muscle mass” when providing an overview and discussion of the topic and will use the terminology described in Table 1 when referring to specific research findings. The latter will reflect the compartment being assessed by the body composition technique used in the study.

Several cutpoints have been used to define “low” muscle mass. We present the most commonly used ones in Table 2, although this list is not exhaustive. The term “sarcopenia” has often been used to describe low muscle mass in clinical settings. However, the term is now widely accepted to also include measures of strength, muscular performance, or physical performance [1,2] and usually used in context of ageing. Notably, cutoffs for low muscle mass are mostly derived from relatively healthy cohorts and hence are of limited applicability to different patient populations and clinical settings. However, they provide a benchmark for quantifying degrees of muscle depletion as it correlates to changes in health status. The absence of standardized diagnostic criteria for low muscle mass precludes a more comprehensive characterization of the prevalence and significance of this condition among different cohorts of patients, an issue discussed later in this review.

Low muscle mass is not restricted to individuals with a small frame, Figure 1(a,b). The concurrent appearance of low muscle mass with high adiposity (also termed sarcopenic obesity) is the new face of an old problem, common in people who face chronic diseases. This condition has a compounding impact on health and outcomes. To date, medical practice relies on measures of body size such as BMI; however, BMI does not necessarily relate to muscle mass, a limitation that may impact the ability of healthcare professionals to carry out targeted interventions directed at addressing low muscle mass rather than interventions focused on addressing adiposity. The prevalence of low muscle mass relates to age, sex, diet, physical activity, disease state and hormonal regulation and other metabolic abnormalities in both obese and non-obese states.

Although most studies to date have only quantified muscle mass, the “quality” of the muscle is also a determinant of outcomes. This feature is assessed by the amount of fat infiltration in skeletal muscle (myosteatosis) using computerized tomography (CT) or magnetic resonance imaging. CT images provide measures of macroscopic intermuscular fat and muscle attenuation, the latter of which is inversely associated with muscle fat content [3] The lower the muscle attenuation or radiodensity, the higher the amount of fat infiltration into muscle. This feature is an emerging prognostic indicator although primarily studied under the auspices of cancer, where imaging techniques are available for its assessment.

Selected techniques available for the estimation of the muscle mass compartment have been described elsewhere [4,5]. The reader is referred to previous articles for a comprehensive discussion of the benefits and limitations of available body composition techniques [6].

**Table 2. Common cut-points to define low muscle mass.**

| Method                                    | Cut-points                                                                 |
|-------------------------------------------|---------------------------------------------------------------------------|
| L3 skeletal muscle index (cm²/m²):         | • ≤ 52.4 for men, ≤ 38.5 for women [109]                                  |
|                                           | • ≤ 43 for men with BMI ≤ 24.9 kg/m², ≤ 53 for men with BMI > 24.9 kg/m²,  |
|                                           | • ≤ 41 for all women [221]                                                |
| Study-specific cut-points (e.g. tertiles)  | Cross-sectional area of psoas muscle at L4                                 |
| L2 skeletal muscle size (cm²)              | Study-specific cut-points                                                 |
| Study-specific cut-points                  | Cross-sectional area of psoas muscle at L4                                 |
| Appendicular skeletal muscle index (kg/m³):| • 7.26 for men, 5.54 for women [222]                                      |
|                                           | • ≤ 7.25 for men, 5.67 for women [223]                                    |
|                                           | • < 7.23 for men, 5.67 for women [224]                                    |
| Appendicular skeletal muscle index (kg/m²):| ≤ 8.87 kg/m² for men.                                                       |
| Muscle mass calculated from resistance or  | < 6.42 kg/m² for women [225]                                               |
| manufacturer proprietary calculations      | Skeletal muscle index: < 10.76 kg/m² for men,                              |
|                                           | ≤ 6.76 kg/m² for women [226]                                               |

BMI: body mass index.
to highlight how the field has evolved into the current state of knowledge and how this has shaped current understanding of the role of low muscle mass in health care.

We included only studies using body composition techniques and not those using anthropometry (through equations or direct measures). As the purpose of this manuscript was to provide an overview of the most recent literature rather than a systematic review, criteria for selection of the publications were more lenient. Observational studies, longitudinal studies, and clinical trials were included. No exclusion criteria were set other than mentioned above. The search for January 2016–January 2017 publications was conducted exclusively on PubMed yielding 2350 articles. Search terms included those related to muscle mass and clinical outcomes, Supplementary Material.

One hundred and forty-three relevant articles in a single year were selected and are included in our discussion below, highlighting emerging research on the impact of muscle mass in various cohorts (Table 3). Articles were organized by clinical care settings: inpatient (surgery, cardiovascular disease, renal disease, chronic obstructive pulmonary disease [COPD], critical illness, “other”), outpatient (cancer, liver conditions, and primary care/population) and long-term care. Not all publications provided sufficient details regarding the study cohort; as such, samples of individuals undergoing surgery or any other procedure that typically requires at least one inpatient day are discussed in the context of inpatient (vs outpatient) settings. As discussed above, the terminology herein will refer to specific compartments being measured/estimated when discussing specific study findings (per Table 1), except when discussing the assimilated data in general terms/collection of evidence.

### Inpatient settings

Low muscle mass in hospitalized patients is a prevalent phenomenon that worsens with increased time spent admitted to a hospital [7]. This is led by a variety of reasons ranging from hyper-catabolism, inadequate food intake and/or immobility, depending on the condition being investigated. The ability to conduct in-depth body composition assessments in inpatient settings has contributed to a large number of investigations, including recent ones. We identified 79 articles that examined the relationship between muscle mass and outcomes published within the timeline described above. These included the following settings and conditions: surgical ($n=49$), heart

| Table 3. Summary of studies in a single year assessing the effect of muscle mass on clinical outcomes. |

| Muscle mass/radiodensity as a positive impact | Muscle mass/quality as a null impact |
|-------------------------------------------|------------------------------------|
| Inpatient  |
| Surgery   | Survival                           | Survival                           |
|           | Post-operative complications       | Post-operative complications       |
|           | Length of stay and readmission     | Quality of life                     |
| Heart disease/conditions                   | Survival                           |
| Renal     | Length of hospital stay             | Survival                           |
| COPD      | Physical function                  | Survival                           |
| Critical care/ICU                          | Disease-specific variables         | Quality of life                     |
| “Other”  | Ventilator support                 |                                     |
| Outpatient                                    |                                     |
| Cancer   | Survival                           | Survival                           |
| Liver conditions                             | Treatment toxicity                 |
| Primary care                                  | Number of treatment cycles         |
| Population                                    | Disease progression                |
| Long term care                                | Survival                           |
| COPD: chronic obstructive pulmonary disease; ICU: intensive care unit; NYHA: New York Heart Association.
conditions \( (n=10) \), renal disease \( (n=5) \), COPD \( (n=2) \), critical illness \( (n=6) \) and other conditions not otherwise specified \( (n=7) \) among hospitalized patients.

**Surgery**

Approximately 9.7 million inpatient surgical procedures occur in the United States each year [8]. Identifying potential modifiable risk factors for complications and mortality is essential for optimal post-surgical care, such as immune status, nutritional status and muscle mass. Surgery invokes a catabolic environment and alterations in nutritional status possibly driven by nausea, vomiting, decreased appetite, etc. [9], creating an environment conducive to muscle loss.

Low muscle mass is an economic burden to the health care system, as this condition is associated with an average increase of over $14,000 in total hospital costs per patient undergoing major abdominal surgery compared to patients with normal muscle amounts [10]. Post-surgical complications such as sepsis, infection, prolonged ventilation and pneumonia are reported to occur at a higher rate and survival is shorter in individuals with low muscle mass undergoing different types of surgery [11]. In patients with colorectal cancer and documented low muscle mass, hospital length of stay is longer, the infection risk is greater and more inpatient rehabilitation care is required than in patients with normal muscle mass [12]. Furthermore, having low muscle is an independent predictor of post-operative infections and rehabilitation care among hospitalized older adults \( (\geq 65 \text{ years old}) \) [12]. Low muscle mass is also associated with a higher incidence of surgical complications and shorter survival in numerous different cancer types [13]. In response to the significant burden of this condition, some programs have implemented preoperative lifestyle interventions that incorporate exercise, nutrition interventions, stress reduction, smoking cessation and spirometer exercises [14]. The effectiveness of each intervention is still unknown but has been embraced by patients awaiting surgery [14].

**A year at a glance**

Fourty-nine studies reported the impact of muscle mass on outcomes in surgical patients; most \( (n=44, 89.8\%) \) used CT images, four used bioelectrical impedance analysis \( (BIA, \text{reporting fat-free mass or estimated skeletal muscle}) \) and one used dual-energy X-ray absorptiometry \( (DXA, \text{reporting fat-free mass}) \). The majority of these publications \( (n=26, 53\%) \) were conducted in individuals with cancer. The remaining studies included diverse patient populations comprising of individuals undergoing surgery for liver or lung transplant, upper abdominal surgery, spine surgery, proctocolectomy, hip arthroplasty, intrahepatic porto-systemic shunt placement, pancreaticoduodenectomy, pancreatic resection, aneuryism or general gastrointestinal resection. Of these, 28 studies investigated the impact of muscle mass on survival and most \( (n=22; 78.6\%) \) reported a positive association between survival and muscle mass [15–36]. One publication reported that low muscle mass was not associated with survival in multivariate analysis (only in univariate analysis) [37], and another found that low muscle mass was prognostic of survival only in the presence of obesity [38], suggesting that disease factors and/or excess adiposity might work synergistically with muscle to predict outcomes. Four other publications reported no association between the amount of muscle mass and survival in individuals undergoing nephrectomy for kidney cancer [39], pancreaticoduodenectomy [40], esophagectomy [41] or left ventricular assist device implantation [42]. The lack of an association could be partially explained by the patients included, who may have experienced body composition changes after neoadjuvant therapy [41] or who had advanced cancer [39]. One of the studies that found no association between muscle mass and overall survival also reported that higher muscle attenuation \( (\text{i.e. better muscle quality}) \) was associated with longer survival [40].

Post-operative complications were additional common outcomes found to be associated with low muscle mass or attenuation in 18 studies [28,32,34,36,38–40,43–53], except for one [43], possibly due to the high rates of complication in the entire sample. Low muscle attenuation [24] and low muscle mass [47,54,55] were associated with longer length of hospital stay and hospital readmissions [34,44,48,56,57]. Other outcomes that were reported to be associated with low muscle mass included general morbidity [24,34,41], surgical complications [58], reduced physical function [57,59], lower quality of life [59], higher inflammatory response after surgery [60], discharge destination to a nursing or rehabilitation facility [34,56] and higher hospitalization costs [10,61,62]. One study reported a null association between muscle mass and quality of life post-discharge [63]; although the population was large \( (n=215) \), and diagnoses within the sample were diverse (cancer and non-cancer patients), which could have concealed significant sub-group associations.
In sum, individuals undergoing surgery have diverse clinical backgrounds. Nevertheless, low muscle mass and attenuation have been associated with shorter survival and worse post-operative complications, among other negative outcomes, in most studies.

**Cardiovascular disease/conditions**

Cardiovascular disease is a leading cause of death worldwide. Heart failure, in particular, is highly prevalent, affecting approximately one in five adults during their lifetime [64] and might trigger substantial loss of muscle mass.

Obesity is a risk factor for heart disease, and many patients, therefore, have obesity at disease presentation. However, body weight may be artificially elevated due to edema and can conceal underlying low muscle mass. This influences body composition measurement since hydration may affect some measures of muscle mass. Nevertheless, the presence of low muscle mass is estimated to occur in almost 20% of patients with stable heart failure [65]. It is associated with a decline in several functional parameters such as strength (handgrip and quadriceps), total peak VO₂, walking distance (6-meter walk tests) [65], abnormal cardiac parameters and cardiac perfusion [66].

**A year at a glance**

Ten articles investigated the association between low muscle mass with clinical outcomes in heart diseases/conditions in acute care settings. All studies except one (DXA) reported muscle mass using CT images. The patient populations of interest included individuals undergoing procedures such as transcatheter aortic valve implantation, aortic aneurysm repair or left ventricular assist device implantation. Higher muscle mass was associated with improved overall survival in most [30–33,50,67], but not all studies [42]. Though low muscle mass was not associated with overall survival in one publication, patients with lower muscle had higher rates of inpatient death or prolonged length of hospital stay [42]. Compared to low muscle, having a higher muscle mass was also positively associated with better physical function [49, 68,69], New York Heart Association score [33], fewer post-operative complications [32,50], shorter length of stay [42,49,69] and less ventilator support [32]. Among these discussed, low muscle mass was a negative prognostic factor in cardiovascular disease.

**Renal disease**

In individuals with chronic kidney disease (CKD), systemic inflammation, transient catabolic comorbidities, nutrient losses during dialysis, endocrine abnormalities (such as resistance to insulin, growth hormone and insulin-like growth factor), hyperglycemia, hyperparathyroidism and loss of blood during hemodialysis are prevalent [70]. Additionally, reduced protein diets of 0.6–0.8 g/kg/day may be recommended to patients, not on dialysis. These factors contribute to muscle wasting, which is usually reported under the auspices of protein-energy wasting [70]. In individuals undergoing dialysis, old age, comorbidities, subjective global assessment score >1, inactivity, low albumin and inflammation (C-reactive protein) were associated with low handgrip strength but not with low muscle mass measured by DXA [71]. In the same study, body composition alone was not associated with poorer survival; however, low strength alone (hazard ratio [HR] 1.98, 95% confidence interval [CI]: 1.01–3.87, \( p=.04 \)) or in combination with low muscle mass (HR: 1.93, 95% CI: 1.01–3.71, \( p=.04 \)) was more strongly associated with higher mortality [71]. These findings suggest that strength and muscle mass – while highly related – are two entities differently affecting outcomes in this population.

**A year at a glance**

A variety of body composition techniques were used in patients with CKD including CT images, DXA, BIA, bioelectrical impedance spectroscopy and magnetic resonance imaging. In these studies, higher muscle mass was associated with better physical function [72,73]; both the amount of muscle mass [74] and muscle attenuation [75] were indicative of better survival, although another study reported no associations [76]. In the latter publication [76], all patients had sarcopenic obesity and were actively undergoing maintenance hemodialysis, and no standard cut points of low muscle mass could predict survival. Overall, these studies suggest that muscle mass is associated with poorer outcomes in renal disease patients, but the effect of obesity and other confounders such stage of the disease might mitigate these associations.

**COPD**

Weight loss is common in individuals with COPD, instigated by the difficulty of eating [77] and higher energy expenditure [78,79]. Fat-free mass represents a large portion of this weight loss, as 15–40% of COPD
patients are reported to have low fat-free mass [80,81]. Patients with COPD are also three times more likely to have low fat-free mass with obesity (sarcopenic obesity), poor physical performance (i.e. lower 6-minute walk test distance) and higher systemic inflammation [82].

A year at a glance
Recent clinical evidence demonstrates that individuals with COPD with higher muscle mass (measured by BIA or DXA) experienced better outcomes (e.g. improved forced expiratory volume and COPD assessment test score and reduced dyspnea) [83] and lower occurrence of osteopenia/osteoporosis than COPD patients with low muscle mass [84]. Importantly, the prevalence of low muscle mass was higher in men with COPD compared to matched males with normal lung function. There was a relationship between muscle mass and airflow limitation [84], which suggests that disease severity may induce or exacerbate muscle loss in individuals with COPD. The studies in the past year show that muscle mass is a predictor of important disease-specific outcomes.

Critical illness
Almost 6 million individuals are admitted to intensive care units (ICU) in the United States each year. The most frequent reasons for admission include respiratory system issues with ventilator support required, acute myocardial infarction, intracranial haemorrhage or cerebral infarction, percutaneous cardiovascular procedure with stent and sepsis [85].

The stress response to trauma induces a negative protein balance and resistance to anabolic signals; this reaction, along with physical inactivity [immobility] ultimately leads to proteolysis and loss of muscle mass [86]. Up to 63% of individuals admitted to the ICU on ventilator support have low muscle mass [87], and this percentage is higher in patients ≥ 65 years old [88]. Muscle wasting is likely to worsen during the hospital stay due to considerable systemic inflammation, pre-existing comorbidities, multi-organ dysfunction and prolonged bed rest [89]. Numerous studies have shown that low muscle mass is associated with lower ventilator-free and ICU days [88] and shorter survival [87,88,90].

A year at a glance
In six studies evaluating the critical illness population, muscle mass was usually measured via CT images; one study used BIA-derived phase angle, which is an indicator of cell membrane function and nutritional status [91]. Higher muscle mass or muscle attenuation was unanimously associated with better survival [91–96]. More specifically, greater muscle attenuation was associated with lower 6-month mortality (HR per 10 Hounsfield units: 0.640; 95% CI: 0.55–0.72, p < .001) in mechanically ventilated critically ill patients, after adjustment for the Acute Physiological, Age and Chronic Health Evaluation (APACHE) II score, BMI and muscle mass [94]. Phase angle was predictive of 28-day mortality (OR: 0.63, 95% CI: 0.78–0.96, p = .008) in individuals in the ICU [91]. Trauma patients (n = 23,622) in the lowest quartile of muscle mass had over nine times greater odds of death compared to those in the highest quartile (OR: 9.15, 95% CI not reported, p < .001) [93]. In terms of outcomes other than survival, two studies reported an inverse association between length of stay and muscle mass [92] and density [94]. In emergency surgery, higher muscle mass was predictive of lower surgical morbidity, but not survival in multivariate analysis [92]; however, this study used only psoas muscle, which may not be representative of whole-body skeletal muscle [97]. Overall, both the amount of muscle mass and attenuation are usually indicative of survival and other clinical outcomes.

Other conditions
Individuals with aspiration pneumonia, abdominal wall hernias and pancreatic disease are also inpatients, and at risk for muscle loss (measured by BIA in four studies and CT images in two studies). In general, higher muscle mass was associated with better outcomes such as physical function [98], disease-specific outcomes (pancreatic exocrine insufficiency) [99], less dysphagia [100,101], shorter length of stay [102] and survival [103,104].

Outpatient settings
Cancer
Individuals with cancer make up a large proportion of patients receiving care in outpatient settings. The tumour-bearing state often induces metabolic alterations such as anorexia, hypoanabolism or hypercatabolism [105,106], which might elicit dramatic changes in body composition.

As obesity is a risk factor for certain types of cancer, many newly diagnosed patients have obesity, and up to 15% of patients with obesity have low muscle mass
Low muscle is associated with worse prognosis including poorer quality of life and function [108], severe treatment toxicity, more postoperative infections and complications, incidence of hospitalization, longer length of hospital stay and shorter survival [108–110].

CT images are regularly obtained for diagnostic and follow-up purposes and are an opportunistic method to accurately assess muscle mass, usually using the 3rd lumbar vertebra as a landmark [111]. The availability of these images allows for a large number of studies exploring the association between muscle mass and patient outcomes. Additionally, the assessment of muscle attenuation is also possible; CT-assessed low muscle attenuation is of emerging importance as it may relate to even higher indication of poor patient prognosis, as discussed elsewhere [110,112,113].

A year at a glance

Twenty-five of the studies in outpatient populations were in oncology; all of them included measurement of muscle mass using CT images. Many of these publications found that higher amounts of muscle mass were associated with improved survival [114–127]. Others reported a statistically significant association between survival and intramuscular adipose tissue [125,126,128–131]. Few studies found a significant association only in sub-groups of patients, such as those with a high neutrophil/lymphocyte ratio in males with small cell lung cancer [132], disease with lymph node involvement in individuals with esophageal squamous cell carcinoma [58] or pancreatic cancer patients with a BMI $\geq 22$ kg/m$^2$ [133], suggesting that disease status and body weight might influence the impact of muscle mass on survival. One study reported only a trend towards significance for the association between muscle mass and survival [134], and another found that muscle mass was predictive of survival only in univariate analysis [97]. In the outpatient oncology setting, only one investigation reported no association between body composition and survival in advanced non-small cell lung cancer [135].

Treatment toxicity [135,136], poorer radiographic and objective response to therapy [117], fewer treatment cycles completed [134], and shorter time to tumour progression [135] were also associated with low muscle mass. Some studies reported no association of muscle mass or attenuation and the following outcomes: time to disease progression [135], toxicity to chemotherapy [135] and objective response to therapy [117]. However, these studies were either carried out in advanced cancer patients with almost 10% weight loss in six months [135] or were in a sample that reported high muscle density was associated with radiographic complete response, but not objective response rates [117]. Therefore, body composition is still a useful tool for predicting outcomes in outpatient cancer settings.

Cancer research in one year shows that while low muscle mass might predict lower survival in most studies, factors such as inflammation, disease stage, and BMI might mitigate this relationship. Body composition might also relate to other prognostic outcomes.

Liver diseases

Liver conditions largely comprise of cirrhosis and liver disease. Cirrhosis is a highly catabolic condition due to insufficient liver glycogen storage, metabolic patterns are similar to that observed in healthy individuals after 2–3 days of starvation [137]. Of particular concern is high use of amino acids as fuel, leading to the breakdown of muscle tissue.

Up to 43% of patients with cirrhosis have low muscle mass, 20% have low muscle concurrent with obesity (sarcopenic obesity), and 52% have low muscle attenuation [138]. Importantly, patients with any body composition abnormality have shorter survival compared to patients with normal body composition [138].

A year at a glance

Five studies investigated the impact of muscle mass on outcomes in liver conditions, using muscle mass from CT images ($n=3$), estimated muscle mass from BIA data, ($n=1$), or both ($n=1$). In these individuals, low muscle mass was associated with worse albumin levels [139], Child-Pugh scores [139], physical function [140] (correlation only) and shorter survival [138,141,142]. Body composition in these studies was, therefore, a useful tool for prognostication.

Primary care and population

Body composition abnormalities such as low muscle mass can occur across age, sex and BMI groups [143]. Hence, it is plausible that a seemingly healthy individual might have low muscle mass. Research on the implications of low muscle mass is limited in younger adults. Instead, community-dwelling older adults are the most common population studied in primary care and population-level investigations. As such, low
Low muscle mass has been associated with increased risk of falls, osteoporosis, hospital re-admission and difficulties in activities of daily living [1]. At the same time, fat mass increases until the sixth decade of life [143], increasing the risk of these individuals to develop sarcopenic obesity.

Among older adults, men often have higher rates of low muscle mass than women [144], due in part to the higher amounts of muscle men have earlier in life. However, the mortality risk is higher in women with low muscle [144]. This is likely because women have higher fat mass and lower muscle mass and strength than men, increasing their risk of developing functional decline.

Physical function is also critical in older adults, as measures such as grip strength and gait speed are inversely associated with disability and mortality [145,146]. In fact, some suggest that these measures are a different construct than muscle mass [147], and including measures of physical function might be more predictive of negative outcomes than measures/estimations of muscle mass alone [146,148]. The term sarcopenia is used in this setting when both low mass and function/performance are taken into account [1,2].

**A year at a glance**

Twenty articles investigated low muscle mass in primary care, mainly in healthy community-dwelling older adults. Muscle mass was measured using BIA (n = 9), DXA (n = 7), CT images (n = 3) or magnetic resonance imaging (n = 1). Higher muscle mass and not having sarcopenia was positively associated with serum albumin levels [149] better physical function [150–159], higher quality of life [157,159] and longer survival [154,160–162]. Higher muscle mass was also negatively associated with cardiovascular disease risk factors [163], idiopathic pulmonary fibrosis [154], low bone mineral density [164], bone fractures [165], hospitalization [161], poor pulmonary function [166]; sarcopenia was associated with poorer disease-specific outcomes such as ankylosing spondylitis [164] and poor renal function [167]. Better muscle attenuation was associated with improved balance [150], quality of life [159] and survival [162]. Notably, one study [168] found no association between estimated muscle mass (from BIA) and quality of life in older adults; only physical activity, handgrip strength and balance were associated with overall quality of life. In older individuals, strength declines more rapidly than muscle mass and factors such as muscle attenuation, metabolism, aerobic capacity, insulin resistance, fibrosis and neural activation might be more relevant for physical function and impaired mobility (and thus the quality of life) than muscle mass alone [169–171].

The impact of muscle mass and sarcopenia on patient/healthcare outcomes has also been investigated on a population level (mainly community-dwelling mid-dle-age or older adults) in fourteen studies, which primarily utilized DXA alone (n = 10) or in combination with air displacement plethysmography (n = 1), followed by BIA (n = 2) and CT images (n = 1). Survival was longer in those with more muscle mass [172–177]. Sarcopenia was associated with lower bone mineral density [178] and osteoporosis risk [179], and low muscle mass was associated with poor pulmonary function [180] and physical function [179,181], and higher fracture risk [182,183], frailty [181], and morbidity [184]. One study reported that slow walking speed, but not low muscle mass was associated with increased risk of hospitalization or higher likelihood of short-term nursing facility stay in women aged ≥65 years [185].

The outcomes assessed in this group of individuals are diverse. Although low muscle mass is predictive of many of these outcomes in primary care and population level settings, the interplay between other ageing-related factors (e.g. hormonal changes, muscle energetics, neural connectivity, muscle blood flow, etc.) is also thought to contribute to mobility-disability in this population.

**Long-term care settings**

The pathophysiology of low muscle mass in long-term care residents is multi-factorial and consists of morphological changes (e.g. type II muscle fiber loss), hormonal changes (e.g. lower testosterone, estrogen and growth hormone), higher inflammation/oxidative stress and lifestyle influences (low physical activity and energy intake) [186]. Comorbidities such as heart disease, dementia and Parkinson’s disease are common and contribute to further nutritional decline [187].

Low muscle mass in long-term care is most often investigated as a construct of sarcopenia (i.e. low mass and function). Sarcopenia in individuals in long-term care is more prevalent than in community-dwelling adults [188]. In individuals age 70 years and older, over one-third have sarcopenia and this condition is associated with a higher risk of death compared to residents without sarcopenia after adjusting for age, sex, physical impairment, BMI and a number of comorbidities (HR 2.34, 95% CI 1.04–5.24) [189].

**A year at a glance**

Dual X-ray absorptiometry (n = 5) and BIA (n = 2) were the only measurement methods used in seven studies
in the long-term care setting. Cognitive function was the most frequently reported outcome, and most did not find any association between sarcopenia and this parameter [190–191]. Activities of daily living were found to be associated with muscle mass and sarcopenia in two studies [192,193], but not another [191]. Mixed findings were also apparent when the relationship between muscle mass [193] or sarcopenia [191] and nutritional status as measured by the Mini Nutritional Assessment was investigated (positive relationship [193]; null [191]). Individuals with lower muscle mass had worse Alzheimer’s severity [194] and individuals with sarcopenia had poorer survival [195]. A year of research had no conclusive evidence for a diverse array of outcomes.

Treating low muscle mass: Addressing an unmet medical need

The above discussion, complimented by a one-year glimpse at publications, showcases the rapidly growing research of body composition in clinical settings. As we discuss, low muscle mass is prevalent across the continuum of care and is a predictor of poor outcomes. Therefore, the potential clinical benefits of preventing and reversing low muscle mass in patients are likely to impact not only patient outcomes but also resource utilization/health care costs [61,196–198].

Some clinicians may question the anabolic potential of patients who suffer from acute or chronic conditions associated with muscle loss. However, evidence suggests that interventions can help to maintain or rebuild muscle in these patients [199]. For instance, cancer patients were found to have a normal anabolic response to nutrition interventions [200], not differently than healthy persons [201], even after surgery [202]. Also, in patients with COPD, the anabolic response to nutrition is not different from that of healthy individuals [203].

New perspectives

The availability of body composition techniques is still limited in clinical settings. Nonetheless, as the value of assessing muscle mass and mitigating muscle loss emerges, so will the recognition of its use for adequate patient screening and monitoring, and we anticipate a surge of technological developments and financial investments. The recent establishment of ICD-10-CM code for sarcopenia by the Centers for Disease Control and Prevention highlights the momentum for such change in perspective and practice. With the establishment of the ICD-10 code in the US, muscle loss as sarcopenia is now recognized as a condition that can be documented and reported within the healthcare setting and for data collection. The code, M62.84, is now available for use by the medical community effective 1 October 2016. The new code designation for this condition has the potential to affect research and development of treatments. It calls into action a need to establish clear clinical guidelines for diagnosis, early intervention and treatment of muscle loss. It will potentially enable development and reimbursement of diagnostic tools to measure muscle mass. It also opens new avenues for development of novel therapeutics targeting muscle loss that could receive FDA approval. Having an ICD-10 code will also enable data capture from electronic medical records, death certificates and other system data sources, which will help the understanding of health economics associated with this condition, also helping researchers to access this data more easily. Overall, the ICD-10 code gives validity to the importance of muscle mass in driving long-term health benefits across the continuum of care.

Where do we go from here?

With this increasing evidence on the importance of maintaining muscle mass in various clinical settings, it is critical to develop effective health screening tools to identify people at risk of losing muscle. Tools such as the SARC-F (strength, assistance in walking, rise from a chair, climb stairs, falls) questionnaire [204] are quick and valid [205] in older individuals, but the psychometric properties of such instruments in clinical populations has not been determined. In addition, there is a need for clinically viable tools to measure muscle mass (and attenuation) at the bedside and develop early intervention strategies to mitigate muscle loss. Currently, body composition measurement tools (e.g. DXA, CT) although available to specific clinical settings are not widely available to the general population. Hand held tools such as ultrasound and BIA show promise [206] and are in various stages of validation in different clinical settings. Measurements of muscle function such as grip strength are very good predictors of mobility limitations in older adults, as previously discussed [207]. Therefore, regulatory agencies have suggested improvement in both muscle mass and physical function or survival as endpoints, although these outcomes are ambiguous [208,209].

For such tools to become routine in clinical practice, healthcare professionals need to be educated on
the importance of muscle loss, and how to incorporate routine screening and intervention for these conditions into their clinical practice. For example, screening for muscle loss could be included as part of the Welcome to Medicare and annual Medicare wellness preventive exams in the United States.

In order to provide a foundation for clinical measurement of body composition, a consensus definition of low muscle is needed for various clinical populations. The use of CT images has been recently popularized due to its widespread availability. Total muscle cross-sectional area at the 3rd lumbar vertebrae is highly correlated with whole-body muscle mass [210] and is often used to identify low muscle. The use of a single muscle group (e.g. psoas) is a new trend in body composition assessment. However, this methodology is poorly correlated with total skeletal muscle area and may impede correct interpretation of prognosis [97]. Furthermore, this particular muscle might atrophy due to comorbidities such as low back pain or hip osteoarthritis independent of surrounding musculature [211,212]. Some research suggests using linear measures of two muscle groups (psosas and paraspinal muscles) in combination with age and sex can accurately identify individuals with low muscle mass [213], although alternative measurements of total muscle cross-sectional area have been strongly discouraged [214].

Although CT images using total muscle cross-sectional area at the third lumbar vertebra offer an accurate assessment of whole body skeletal muscle mass, certain conditions (i.e. critical care settings) limit weight-bearing activity and are associated with disproportional muscle atrophy in the lower limbs [215]. Therefore, the accuracy of CT images for whole-body muscle may be compromised, although little is known on this topic. Furthermore, CT imaging may not be sensitive enough to detect body composition changes in short time periods [216]. Ultrasound is emerging as the method of choice for such settings where selected muscle groups can be assessed individually [217], although protocols for accurate assessment are still underway.

There is a considerable need to counteract the loss of muscle mass, strength and physical function. Possible dietary interventions might include protein/amino acid formulas, creatine, β-hydroxy-β-methylbutyrate and micronutrients, among others. Exercise typically consists of strength or aerobic activity in a supervised or home-based intervention. A recent systematic review concluded that exercise improves muscle mass, strength and physical performance in healthy adults 60 years and older with additional benefit of nutrition in a small proportion of studies [218]. The purported limited effectiveness of nutrition could be due to the great heterogeneity in the type and duration of dietary supplement protocols. Future well-designed clinical trials that combine some form of nutrition and exercise such as the Multimodal Intervention for Cachexia in Advanced Cancer Patients Undergoing Chemotherapy (MENAC) [219] and Nutrition and Exercise in Critical Illness (NEXIS) [220] will elucidate the potential feasibility and efficacy of methods to counteract muscle loss.

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