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# Risk factors for 5-year mortality in a cohort of elderly patients with sarcopenia

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ABSTRACT

*Background:* The association between multiple risk factors and the mortality of sarcopenic patients has not been studied. This study's aim is to report the prevalence of sarcopenia among a sample of Italian hospitalized older adults, describe the physical function, body fat composition, cognitive, inflammatory and nutritional status of sarcopenic compared with non-sarcopenic subjects, and determine the risk factors associated with mortality in sarcopenic patients.

*Method:* A total of 462 patients were enrolled and followed up for a period of 5 years. Sarcopenia was diagnosed according to the EWGSOP2 criteria. Factors associated with sarcopenia were identified with linear regression analysis. Logistic regression was applied to explore the association between the risk factors and mortality in sarcopenic subjects. Survival analyses and predictors of mortality were identified using Kaplan-Meier and Cox regression.

*Results:* The prevalence of sarcopenia was 33.5%. Linear regression showed that sarcopenia was associated with Barthel index (B −9.63, p0.004), BMI (B −3.19, $p < 0.001$) and android fat (B 1.85, p0.004). Of these factors, only the number of co-morbidities (OR 1.394 C95% 1.023–1.862 p 0.025) and MMSE scores (OR 0.857 C95% 0.79–0.930 $p < 0.001$) were associated with mortality in sarcopenia. Kaplan-Meier and the log-rank tests showed the negative prognostic effect of low BMI (p0.007), albumin ($p < 0.001$) and Barthel index (p 0.018). The Cox regression showed that mortality hazard is reduced with BMI > 24.9 (HR 0.287 C95% 0.095–0.866 p 0.027).

*Conclusion:* Sarcopenia is associated with low physical function and BMI but higher android fat. Low Barthel, BMI and albumin can significantly decrease the survival rate in sarcopenic patients. Whereas BMI > 24.9 is associated with lower mortality hazard.

## 1. Introduction

Sarcopenia is the slow, progressive and generalized loss of skeletal muscle mass and strength associated with aging (Cruz-Jentoft et al., 2019). It is recognized as a disease with an (ICD-10-MC) code (Anker et al., 2016). It leads to adverse health outcomes such as physical disabilities, poor quality of life and increased risk of falls, fractures, hospitalization and mortality (Beaudart et al., 2017). It is associated with other morbidities such as Alzheimer's disease (Ogawa et al., 2018), cardiovascular mortality (Brown et al., 2016; Im et al., 2017) and chronic respiratory diseases (Bone et al., 2017).

The consequences of sarcopenia impose a social and an economic burden on societies worldwide, especially that the aging population is increasing globally. Having a low physical performance makes

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sarcopenic patients highly dependent on others for their basic daily activities. This functional impairment increases the costs for health care and hospitalization (Sousa et al., 2016; Liguori et al., 2018; Clark and Manini, 2010). Therefore, in order to minimize this burden by reducing the risks of developing sarcopenia and improving the physical performance of sarcopenic patients, it is essential to understand the mechanisms of this disease and the factors associated with it.

The mechanisms of sarcopenia are complex and multifactorial because the muscle is not only a contractile organ that functions in locomotion; it has also an important role in glucose and protein metabolism in addition to bone density (Hunter et al., 2019). Scientific evidence shows that after the age of 50, the number of functional motor units decrease (Damanti et al., 2019). Aging causes a reduction in the synthesis of muscle proteins and mitochondria. The existing mitochondria lose their enzymes which impairs their function leading to oxidative stress and the accumulation of reactive oxygen species. Altogether, this causes the reduction in muscle strength. Aging is also associated with alteration in neurotransmitters and hormonal dysregulation (such as sex and growth hormones) which may contribute to muscle loss (Tournadre et al., 2019). Research on aging has also shown that it is characterized by chronic inflammation causing tissue damage and organ dysfunction, consequently leading to poor physical function, morbidities and mortality (De Martinis et al., 2006). Malnutrition, particularly inadequate protein intake (Sieber, 2019), along with sedentary lifestyle and the lack of muscle usage accelerates the reduction in muscle mass and function especially in older adults (Welchl et al., 2018).

The prevalence of sarcopenia and its associated factors were examined by several investigators. For example, it was reported that sarcopenia is highly prevalent in a population of Spanish older adults and it was associated with low BMI and Barthel index (Bravo-Jos et al., 2018). More than one third of elderly people living in a Brazilian capital were sarcopenic, most of these were males with low weight (Pelegrini et al., 2018), A study based on a Korean population showed that sarcopenia was higher in participants with diabetes, high cholesterol, osteoarthritis and low vitamin D levels (Bae and Kim, 2017). A systematic review reported a high prevalence of sarcopenia in nursing homes, malnutrition seemed to be an independent associated factor (Yanjiao et al., 2019). The association between sarcopenia and mortality has also been well studied. Sarcopenia was considered as a strong predictor of all-cause mortality in community older individuals (Jung Hee et al., 2014; Arango-Lopera et al., 2013; Björkmana et al., 2019), among nursing home residents (Zhang et al., 2018; Landi et al., 2012a), and hospitalized older adults (Vetrano et al., 2014).

In general, the aforementioned studies, in addition to many others in the literature, have either focused on measuring the prevalence of sarcopenia and identifying the associated risk factors, or examined the relationship between sarcopenia and mortality in specific populations of older adults. However, the key question which has not been addressed clearly is: What is the prognostic effect of the associated factors of sarcopenia? In particular, which risk factor can increase the mortality rate in sarcopenic patients? The answer to this question could help in developing therapies for sarcopenia and improve the prognosis of this disease.

Thus, the aim of this study is to: (1) examine the prevalence of sarcopenia among a sample of Italian hospitalized older adults followed through a time period of five years, (2) compare between sarcopenic and non-sarcopenic subjects according to their physical function, body fat composition, cognitive, inflammatory and nutritional status. (3) explore the association between sarcopenia and possible risk factors, and (4) determine which of these factors are associated with increased mortality risk in patients with sarcopenia.

## 2. Materials and methods

### 2.1. Setting

The study was performed in the city of Pavia (Italy). We evaluated elderly men and women consecutively admitted to our physical medicine and rehabilitation division (Azienda Servizi alla Persona, Santa Margherita Institute). Patients in our hospital are either referred from acute care hospitals in the Lombardia area of northern Italy for follow-up care and/or rehabilitation, or are local residents with chronic conditions associated with elderly age who require revision and updates to their treatments.

### 2.2. Study population

Eligible patients were aged 65 years or older. Subjects not affected by acute illness, severe liver (as defined by ESPEN Guidelines (Plauth et al., 2006)), heart (European Society of Cardiology proposed guidelines for the diagnosis (Vasan and Levy, 2000)), or kidney dysfunction (acute kidney 'risk, injury, failure' as defined by the newly developed RIFLE classification (Hoste et al., 2006)), or severe dementia (MMSE $< 18$ points), (Folstein et al., 1975) and had a body weight that had been stable for 6 months, were included in the study. Moreover, subjects with uncontrolled diabetes, dysthyroidism, and other endocrinopathies, neoplasia, as well as patients treated with steroids, or with total walking incapacity, were excluded. The study design was approved by the ethics committee of the University of Pavia, and an individual written informed consent was obtained from each participant. Data were gathered from the end of January 2011 to the end of January 2016. Study variables were measured at the time of enrollment.

### 2.3. Observed variables

#### 2.3.1. Body composition assessment

Body composition such as Free Fat Mass (FFM), Fat Mass (FM), and gynoid and android fat distributions was measured by dual-energy X-ray absorptiometry (DXA) with the use of a Lunar Prodigy DXA (GE Medical Systems). The in vivo CVs were 0.89% and 0.48% for whole-body fat (fat mass) and FFM, respectively. The Skeletal Muscle Index (SMI) was taken as the sum of the fat-free soft tissue mass of arms and legs, and divided by height2. Whole body and FFM were divided by height squared to obtain FFM index (FFMI). FFM depletion was defined as having whole-body FFMI below the 5th centile for age- and gender-matched healthy subjects (Baumgartner et al., 1998).

Body weight was measured to the nearest 0.1 kg using a precision scale, with the subjects wearing light clothing and without shoes, using standardized technique, and body mass index (BMI) was calculated ($kg/m^2$).

#### 2.3.2. Assessment of bone mineral density

Bone mineral density (BMD) (g/cm2) of the total hip was measured using DXA. BMD was labeled as normal when T-score $> 1.0$, osteopenic if T-score $< -1.0$, and osteoporosis when T-score $\leq -2.5$ (Klein et al., 2005).

#### 2.3.3. Blood sample measurements

Fasting venous blood samples were drawn between 8 am and 10 am, with the subjects in a sitting position. Blood handling and collection were carried out under strictly standardized conditions. Folate and vitamin B12 were determined using an immunoassay, and high-performance liquid chromatography was used to measure total plasma homocysteine levels. Serum albumin was also analyzed using a nephelometric method, with a 2% coefficient of variation. Fasting blood total cholesterol and triglyceride levels were measured by automatic biochemical analyzer. High-sensitivity C-reactive protein and

erythrocyte sedimentation rate were also assessed.

#### 2.3.4. Assessment of functional performance

Handgrip strength was assessed using a Jamar dynamometer adhering to the standardized protocol recommended by the American Society of Hand Therapists. Dominant and non-dominant handgrip strengths were measured with a calibrated dynamometer (Baseline, Elmsford, NY, USA). The grip handle was adjusted to accommodate the size and comfort of the participant's hand, and the elbow was flexed to 90°to guarantee the strongest grip strength measurement (Mathiowetz et al., 1985).

A weak handgrip was defined as < 27 kg for men and < 16 kg for women using the average value of the two handgrip measurements of the dominant hand (Landi et al., 2012b). Low gait speed (≤0.8 m/s both for males and females) is an indicator for defining 'severe sarcopenia' The functional status of each enrolled was determined based on the Barthel index (B_I) score. This scale ranges from 0 (totally dependent) to 100 (totally independent) and assays 10 individual aspects of daily living (Mahoney and Barthel, 1965).

#### 2.3.5. Assessment of cognitive status and mood

The Mini–Mental State Examination (MMSE) is a well validated and widely used assessment of global cognitive function. It takes approximately 10–15 min to administer and has a maximum score of 30 points, with lower scores representing poorer performance. The MMSE includes items assessing orientation, memory, attention, language, and visuospatial capabilities (Folstein et al., 1975).

#### 2.3.6. Assessment of sarcopenia

For the evaluation of sarcopenia we used the EWGSOP2 criteria, sarcopenia is defined as having low handgrip strength (< 27 kg for males and < 16 kg for females) and low muscle mass (< 7.0 kg/m2 for males and < 5.5 kg/m2 for females). Muscle mass was determined by the appendicular skeletal muscle index (ASMI), and calculated by dividing ASM by height$^2$. Gait speed (≤0.8 m/s both for males and females) is an indicator for defining 'severe sarcopenia' (Liguori et al., 2018).

#### 2.3.7. Assessment of mortality

Patient survival was defined as the time between the date of enrolment and the date of death or the date of last contact (censoring). Particularly, vital status was ascertained by means of active follow-up (in-office visits, inquiries by telephone or mail to participants or proxy respondents and linkage to municipal registries).

### 2.4. Statistical analysis

The normal distribution of the data was evaluated by Shapiro-Wilk W test. General characteristics of the sample were explored using independent *t*-test, data were presented as mean values and standard error. The association between sarcopenia and the risk factors was determined using linear regression adjusted for age, gender and all the variables with a significant *p* value ($p < 0.05$) in the t-test. Univariate logistic regression was performed unadjusted for each variable. Then a multivariate logistic regression analysis was constructed adjusted for all the factors with a significant p value from the univariate analysis. Stepwise and forward (likelihood ratio) selection was applied to identify the variables associated with mortality in subjects with sarcopenia. Variables which were significantly different in sarcopenic subjects, were graphed in Kaplan-Meier curves to compare the survival rates at 5 years of follow-up. Log rank test was applied to identify the significant variables, then these were entered into a Cox regression model adjusted for age and gender. All analyses were performed using the Statistical Package for the Social Sciences (SPSS), version 21.0.

**Table 1**
Characteristics of the population according to sarcopenia status.

| Characteristic | Distribution of sarcopenia | | *p*-Value |
|---|---|---|---|
| | Sarcopenia (*n* = 155) | No sarcopenia (*n* = 307) | |
| Age, yrs | 82.23 (0.53) | 80.93 (0.38) | 0.047 |
| Functional status | | | |
| Handgrip (kg) | | | |
| Male (*n* = 135) | 18.76 (1.21) | 21 (0.87) | 0.127 |
| Female (*n* = 327) | 14.51 (0.68) | 15.67 (0.43) | 0.165 |
| Barthel index (points) | 44.82 (2.65) | 64.33 (1.63) | < 0.001* |
| Cognitive status | | | |
| MMSE (points) | 15.76 (0.57) | 16.17 (0.4) | 0.556 |
| Biochemical parameters | | | |
| Albumin (g/dL) | 3.38 (0.05) | 3.71 (0.03) | < 0.001* |
| ESR (mm/h) | 61.64 (2.58) | 42.03 (1.66) | < 0.001* |
| CRP (mg/dl) | 1.81 (0.24) | 1.11 (0.14) | 0.012* |
| Folic acid (ng/ml) | 9.97 (1.47) | 8.48 (0.62) | 0.27 |
| Vitamin B12 (ng/ml) | 656.63 (118.45) | 503.79 (43.52) | 0.228 |
| Triglycerides (mmol/L) | 117.61 (3.73) | 121.52 (3.43) | 0.479 |
| Homocystein (μmol/L) | 19.52 (0.85) | 19.38 (0.73) | 0.91 |
| Anthropometric measure | | | |
| BMI (Kg/m$^2$) | 22.09 (0.32) | 25.64 (0.27) | < 0.001* |
| DXA measurements | | | |
| Osteoporosis femoral t-score | −2.22 (0.13) | −1.97 (0.073) | 0.093 |
| Gynoid fat (%) | 34.54 (0.96) | 38.92 (0.63) | < 0.001* |
| Android fat (%) | 32.39 (1.13) | 35.43 (0.75) | 0.023* |
| Co-morbidities and medications | | | |
| Number of diseases | 6.54 (0.21) | 5.66 (0.16) | 0.001* |
| Number of medications | 9.75 (0.32) | 8.67 (0.21) | 0.004* |

MMSE: mini-mental state examination; ESR: erythrocyte sedimentation rate; CRP: C - reactive protein; BMI: body mass index.Values are given as mean (SE).
* Statistically significant, p < 0.05.

## 3. Results

A total of 462 adults aged 65–99 years (mean: 81.4 ± 0.3 years; 70.6% women) were included in this study. Of these individuals, 33.5% were diagnosed with sarcopenia. The prevalence was higher in males (50.4%) than females (26.6%). During the 5 year follow up 106 individuals died in this cohort. Table 1 shows the general characteristics of this sample. Sarcopenic patient were significantly older, with lower Barthel index, albumin and BMI compared to those without sarcopenia. In addition, sarcopenic patients had higher ESR and CRP levels suggestive of higher inflammatory state; also, they reported higher number of both co-morbidities and medications used. The percent of android and gynoid fat was significantly lower in the case of sarcopenia. Both males and females with sarcopenia showed a lower (but not significant) handgrip strength and bone density.

### 3.1. Risk factors associated with sarcopenia

The results for linear regression of the potentially risk factors indicate that Barthel index, BMI and android fat were significantly associated with sarcopenia (Table 2). In sarcopenic patients, Barthel index was decreased by 9.63 points and BMI was reduced by 3.19 points. Whereas, android fat was increased by 1.85%. The scatter plots between sarcopenia index and these risk factors showed that low BMI had the strongest association with sarcopenia particularly in males (Fig. 1).

### 3.2. Survival analysis of sarcopenic patients

Table 3 shows that the mortality risk for sarcopenic patients increased significantly with increasing age, homocystein levels, number

**Table 2**
Linear regression of the association between sarcopenia and possible risk factors.

| Total n = 155 | | | |
|---|---|---|---|
| Risk factors | B | *p*-Value | $CI_{95\%}$ |
| Age, yrs | 0.71 | 0.439 | (−1.086–2.498) |
| Functional status | | | |
| Handgrip (kg) | | | |
| Male ($n$ = 68) | −2.18 | 0.387 | (−7.270–2.905) |
| Female ($n$ = 87) | 0.138 | 0.926 | (−2.815–3.088) |
| Barthel index (points) | −9.63 | 0.004* | (−16.236 to −3.026) |
| Cognitive status | | | |
| MMSE (points) | −0.38 | 0.709 | (−2.371–1.615) |
| Biochemical parameters | | | |
| Albumin (g/dL) | −0.07 | 0.244 | (−0.179–0.046) |
| ESR (mm/h) | 6.34 | 0.071 | (−0.558–13.243) |
| CRP (mg/dl) | −0.14 | 0.595 | (−0.661–0.379) |
| Folic acid (ng/ml) | 0.13 | 0.942 | (−3.385–3.646) |
| Vitamin B12(ng/ml) | −31.77 | 0.768 | (−243.747–180.201) |
| Triglycerides (mmol/L) | 7.85 | 0.289 | (−6.704–22.398) |
| Homocystein (μmol/L) | −0.43 | 0.798 | (−3.697–2.847) |
| Anthropometric measure | | | |
| BMI ($kg/m^2$) | −3.19 | < 0.001* | (−4.036 to −2.334) |
| DXA measurements | | | |
| Osteoporosis femoral t-score | −0.01 | 0.943 | (−0.343–0.319) |
| Gynoid fat (%) | 0.83 | 0.255 | (−0.600–2.257) |
| Android fat (%) | 1.85 | 0.044* | (0.049–3.655) |
| Co-morbidities and medications | | | |
| Number of diseases | 0.59 | 0.084 | (−0.078–1.252) |
| Number of medications | 0.18 | 0.695 | (−0.723–1.083) |

MMSE: mini-mental state examination; ESR: Erythrocyte Sedimentation Rate; CRP: C - reactive protein; BMI: Body Mass Index; CI: confidence interval. Note: This model is adjusted for age, gender, Barthel index, albumin, ESR, CRP, BMI, Gynoid fat, Android fat, number of diseases and medications.

* Statistically significant, $p < 0.05$.

of diseases and medications used. On the other hand, patients with low levels of blood albumin had 2.6 times higher mortality risk than those with normal albumin levels. Decreasing Barthel index, MMSE score, BMI, gynoid and android fat were associated with higher mortality risk.

Factors from the Univariate logistic regression with a significant p value were used in a multivariate logistic analysis performed with a stepwise and forward (likelihood ratio) selection to determine which of these were associated with increased risk of mortality in sarcopenic patients (Table 4). Low MMSE score and higher number of co-morbidities were significantly associated with mortality in sarcopenia.

As shown in Fig. 2, Kaplan-Meier curves along with log-rank tests indicate that patients with sarcopenia had significantly lower survival rates compared with non-sarcopenic ($p < 0.001$). Among the potential risk factors, BMI, albumin levels and Barthel index significantly affected the survival of sarcopenic patients. After 5 years of follow up period < 50% of the patients who were underweight survived compared with > 60% with normal weight and > 80% with overweight. Patients with low levels of albumin survived less than those with normal levels. Regarding the Barthel index, severe dependent sarcopenic patients showed significantly the lowest survival rates.

The significant variables from Kaplan-Meier log-rank tests were used in the Cox regression analysis adjusted for age and gender. Patients with albumin levels < 3.5, had 1.3 times higher mortality hazard than those with normal levels (p not significant). Barthel index < 21 imposed a higher risk for mortality with a factor of 1.16. Finally, BMI > 24.9 significantly reduced the mortality hazard by a factor of 0.293 (Table 5).

## 4. Discussion

This study, for the first time in literature shows the association between multiple risk factors and the mortality of sarcopenic patients. The prevalence of sarcopenia in this sample is (33.5%), other studies have reported a similar estimation in a Brazilian capital (33.1%) (Pelegrini et al., 2018), in an American sample of community dwelling older adults (36.5%) (Brown et al., 2016), and among an Italian nursing home residents (32.8%) (Zhang et al., 2018). In this study, Sarcopenia was higher in males (50.4%) than females (26.6%). Sarcopenic subjects were significantly older, with lower levels of the following: Barthel index, serum albumin, BMI and body fat compared with those without sarcopenia. Also, sarcopenic subjects showed a higher inflammatory state demonstrated in elevated ESR and CRP levels, as well as higher number of co-morbidities and prescribed medications.

Our findings are consistent with prior work which reported that sarcopenia was less prevalent among obese subjects compared with non-obese (Brown et al., 2016) or individuals with normal weight (Bravo-Jos et al., 2018; Pelegrini et al., 2018; Yanjiao et al., 2019; Vetrano et al., 2014; Malafarina et al., 2019). Low BMI might be the result of malnutrition indicated by low levels of serum albumin in sarcopenic patients in this cohort. Since proteins are the building blocks of muscles, low protein intake can result in low muscle mass associated with sarcopenia. According to Zhang et al., although serum albumin is a useful indicator of malnutrition, it is also one of the acute phase proteins which can be affected by factors other than nutritional status such as inflammation, infection, liver damage and fluid status. Recently, it is recognized that inflammation has an important role in the pathophysiology of malnutrition(Zhang et al., 2017). In this cohort, sarcopenic subjects expressed higher levels of ESR and CRP, therefore, this inflammatory state might have lowered the albumin levels which subsequently resulted in malnutrition. Since Subjects affected by acute illness, severe liver, heart or kidney dysfunction were excluded from this study, it is more likely that the low serum albumin was a result of malnutrition not acute inflammation. This is in accordance with studies which confirmed that protein intake may be a risk factor for sarcopenia (Houston et al., 2008), and higher protein intake is positively associated with improved physical function and muscle strength (Isanejad et al., 2016). In the current study, low BMI showed a significant association with sarcopenia. Moreover, along with low albumin levels, it had a significant detrimental effect on the survival of sarcopenic patients during the follow up period in the unadjusted regression model. After adjusting for age and gender, low BMI but not low albumin remained significantly associated with mortality. On the other hand, overweight sarcopenic patients showed a significantly reduced mortality hazard. However, our findings contradict the results of a study which showed that BMI was not a predictor of mortality among sarcopenic patients (Björkmana et al., 2019) and in a population of Korean older adults which included both sarcopenic and non sarcopenic individuals (Jung Hee et al., 2014).

It is well documented that aging is characterized by an inflammatory phenotype of low-grade so called “inflamm-aging” which initiates or worsens many age related diseases including sarcopenia, and plays a role in shortening the survival in humans (De Martinis et al., 2006). A few studies reported an association between high CRP and the reduction in muscle mass and physical function (Tournadre et al., 2019; De Martinis et al., 2006; Welchl et al., 2018). In our study, although sarcopenic patients showed elevated levels of the pro-inflammatory markers ESR and CRP, the association with sarcopenia was not significant. Furthermore, high ESR and CRP did not alter the survival of sarcopenic patients.

A previous study reported that poor physical function indicated by low Barthel score was associated with sarcopenia in institutionalized older adults (Bravo-Jos et al., 2018), our results confirm this association. In addition, we found that Barthel index ≤60 significantly reduced the survival rate of sarcopenic patients. These results can be

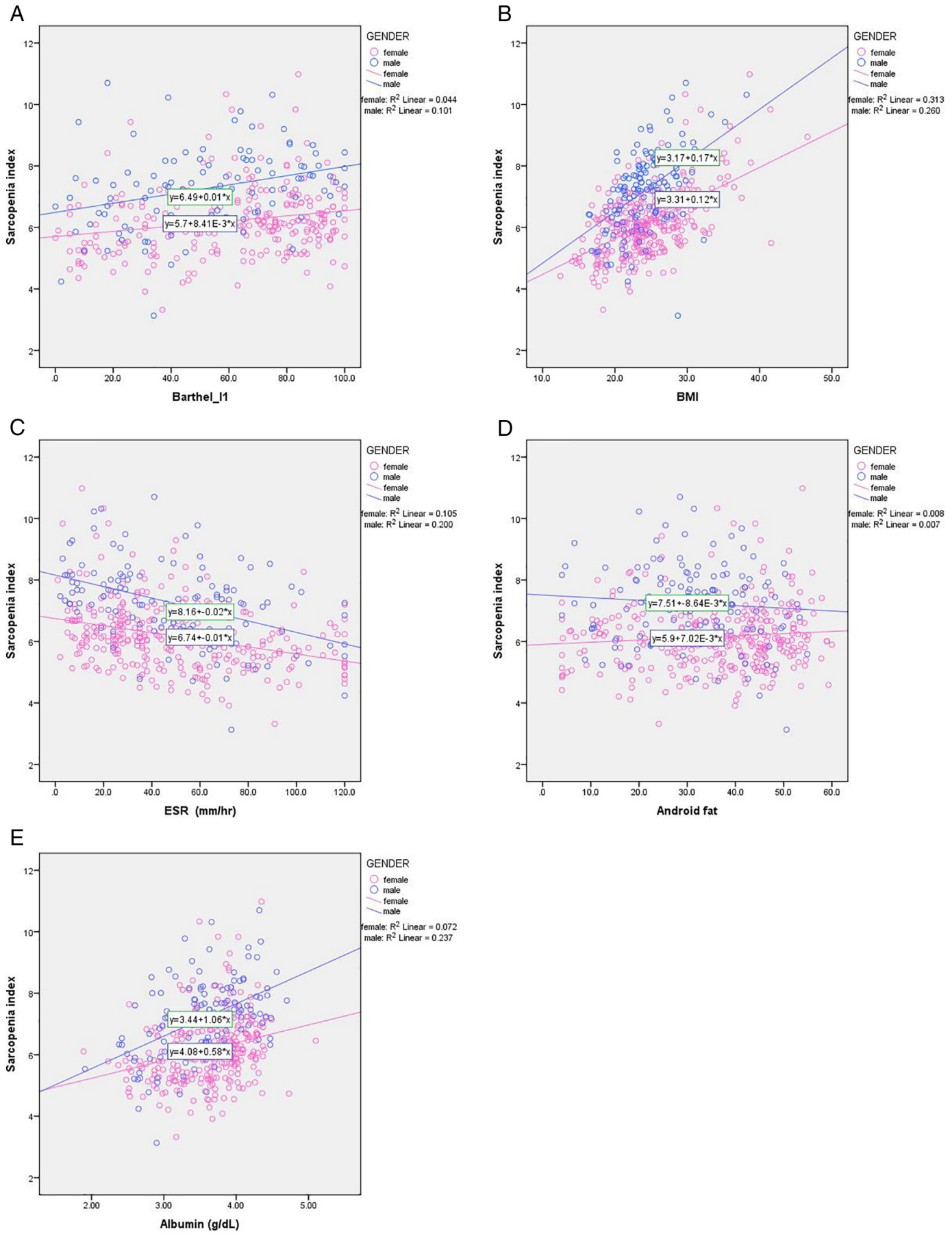


**Fig. 1.** Scatter plots of the risk factors associated with sarcopenia stratified by gender. (a) Barthel index, (b) BMI, (c) ESR, (d) Android fat and (e) Albumin.

**Table 3**
Unadjusted logistic regression analysis of the association between the risk factors and mortality in sarcopenic patients.

| Total ***n*** = 155 | | | |
|---|---|---|---|
| Risk factors | Odds ratio | *p*-Value | $CI_{95\%}$ |
| Age, yrs | 1.089 | 0.003* | (1.028–1.152) |
| Functional status | | | |
| Handgrip (kg) | 0.989 | 0.741 | (0.928–1.055) |
| Barthel index (points) | 0.983 | 0.023* | (0.969–0.998) |
| Cognitive status | | | |
| MMSE (points) | 0.925 | 0.003* | (0.878–0.974) |
| Biochemical parameters | | | |
| Albumin < 3.5 (g/dL) | 2.576 | 0.011* | (1.241–5.346) |
| ESR (mm/h) | 0.997 | 0.561 | (0.985–1.008) |
| CRP (mg/dl) | 1.064 | 0.311 | (0.944–1.200) |
| Folic acid (ng/ml) | 1.002 | 0.890 | (0.971–1.035) |
| Vitamin B12 (ng/ml) | 1.000 | 0.325 | (1.000–1.001) |
| Triglycerides (mmol/L) | 0.997 | 0.424 | (0.989–1.005) |
| Homocystein (μmol/L) | 1.075 | 0.013* | (1.015–1.138) |
| Anthropometric measures | | | |
| BMI ($kg/m^2$) | 0.173 | 0.004* | (0.052–0.574) |
| DXA measurements | | | |
| Osteoporosis femoral t-score | 0.939 | 0.558 | (0.760–1.159) |
| Gynoid fat (%) | 0.971 | 0.042* | (0.943–0.999) |
| Android fat (%) | 0.971 | 0.022* | (0.948–0.996) |
| Co-morbidities and medications | | | |
| Number of diseases | 1.273 | 0.003* | (1.087–1.491) |
| Number of medications | 1.106 | 0.045* | (1.002–1.221) |

MMSE: mini-mental state examination; ESR: Erythrocyte Sedimentation Rate; CRP: C - reactive protein; BMI: Body Mass Index; CI: confidence interval.
* Statistically significant, $p < 0.05$.

**Table 4**
Multivariate Logistic regression analysis of the association between the risk factors and mortality in sarcopenic patients.

| Total n = 155 | | | |
|---|---|---|---|
| Risk factors | Odds ratio | *p*-Value | $CI_{95\%}$ |
| MMSE (points) | 0.837 | < 0.001* | (0.757–0.925) |
| Number of diseases | 1.356 | 0.015* | (1.060–1.734) |

MMSE: mini-mental state examination; CI: confidence interval.
* Statistically significant, $p < 0.05$.

explained by several studies which indicated that physical inactivity can cause reduction in muscle mass and strength, it was found that during a 10 day period of bed rest, healthy individuals lose 1 kg of muscle mass (Kortebein et al., 2007) and in 5 days 9% of quadriceps strength is reduced (Wall et al., 2014).

In this population, the average MMSE score of all subjects (sarcopenic and non sarcopenic) is < 20, indicating a moderate Alzheimer's disease state. Patients diagnosed with sarcopenia however, showed an insignificantly lower MMSE score compared with non sarcopenic individuals. Our results showed that low MMSE score along with increased number of co-morbidities are significantly associated with increased risk of mortality in patients with sarcopenia. Accordingly, previous studies have reported that sarcopenia is highly prevalent in subjects with Alzheimer's disease, and there is a significant correlation between brain volume and lean mass (Ogawa et al., 2018). Alzheimer's disease is listed as a leading cause of death for adults older than 65, it can also lead to disability and morbidity (Association, 2015; Liang et al., 2016).

The unadjusted logistic regression of the association between the risk factors and mortality revealed that in sarcopenic patients, low albumin and high homocystein are associated with an increased risk of mortality. Patients who are sarcopenic with high levels of serum homocystein showed 7 times higher risk of mortality compared to those with normal levels. Ostrakhovitch et al. reported that hyperhomocysteinemia is associated with aging and it contributes to a number of disorders such as cardiovascular diseases, cognitive decline particularly Alzheimer's disease, renal dysfunction and osteoporosis. It is also associated with increased risk of mortality. High homocystein levels can be accompanied with low vitamin B12, because it is an important co-factor in homocystein metabolism (Ostrakhovitch and Tabibzadeh, 2019). However, in our cohort, there was no association between low vitamin B12 and sarcopenia.

Our findings indicate a significant association between sarcopenia and higher android but not gynoid fat. This could be associated by high visceral fat and low gynoid fat. As defined by Perna et al., the phenotype of sarcopenic visceral obesity is characterized by high level of visceral adipose tissue (VAT) associated with elevated levels of IL-6, C-reactive protein, IL-1 receptor antagonist, and soluble IL-6 receptor which could contribute to the development and progression of sarcopenia (Perna et al., 2019). These synergic effects on the muscle could support the rationale of the negative effects that the visceral adipose tissue can exert on the bones. In particular, these negative effects are related to a proinflammatory state that promotes bone resorption. Our sample does not reflect the protective effect of gynoid fat and the related phenotype of sarcopenic obesity. On the other hand, it reflects the combination of low muscle and high visceral fat, which results in a condition defined as sarcopenic visceral obesity. Perna et al. in 2018 reported that inflammation and subsequently sarcopenia are promoted by excess android fat and associated with a greater risk of fractures (Perna et al., 2018). Similarly, sarcopenia was more prevalent in men with abdominal obesity in a population of Korean adults (Bae and Kim, 2017). Also, another study demonstrated a positive association between sedentary life style and waist circumference (Silva et al., 2019). Since sarcopenic patients have low physical activity, this can lead to the accumulation of android body fat which increases the waist circumference.

Ginaldi and De Martinis reported that the low-grade systemic inflammation caused by aging can induce both osteoporosis and sarcopenia by enhancing the apoptosis of osteoblasts and muscle cells (Ginaldi and De Martinis, 2016). Other reports suggested that sarcopenia and osteoporosis are correlated (Kalinkovich and Livshits, 2017; Edwards et al., 2015; Hirschfeld et al., 2017), and that osteosarcopenic individuals have higher risk of mortality (Balogun et al., 2019). However, our results did not align with these reports since osteoporosis showed no significant association with sarcopenia or with mortality in sarcopenic patients, although they have shown an insignificantly lower femoral t-score compared with non-sarcopenic individuals. The mean bone density of both groups is $< -1$ but $> -2.5$ suggesting the condition of osteopenia but not osteoporosis. Is it because they have been treated with supplementations which improved their bone density such as vitamin D and calcium?, we cannot confirm the reason as the type of medications prescribed for these subjects were not identified.

The handgrip strength of the sarcopenic patients was lower but not significant. The non-sarcopenic subjects might have had a weak handgrip due to other co-morbidities such as arthritis, depression, balance disorders or peripheral vascular disorders. Inconsistent with past work which reported that handgrip strength is a predictor of mortality in sarcopenia (Bae et al., 2019), in our study, this association was not significant.

Among all the risk factors analyzed, in the fully adjusted model, the higher number of co-morbidities and low MMSE scores were significantly associated with increased risk of mortality, whereas, BMI > 24.9 is associated with lower mortality hazard. In contrast, a study by *Landi* et al. showed that the co-morbidity burden was not a significant predictor of mortality in an Italian cohort (Landi et al., 2016).

This study has some limitations to be considered when interpreting

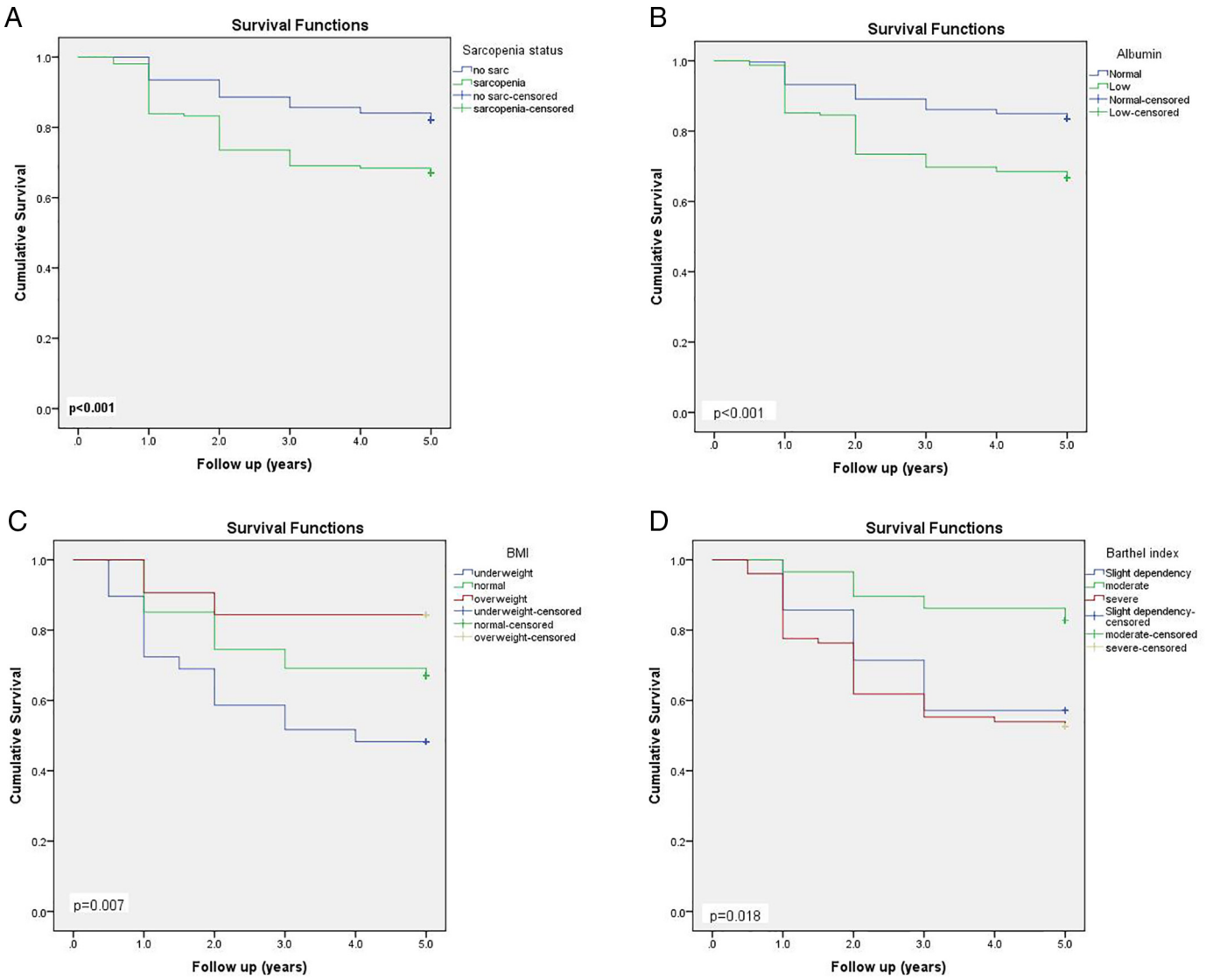


**Fig. 2.** Kaplan-Meier curves (a) Sarcopenic and non-sarcopenic individulas, (b) Sarcopenic patients stratified by BMI categories, (c) Sarcopenic patients stratified by albumin categories, (d) Sarcopenic patients stratified by Barthel index categories.

**Table 5**
Cox regression of the potentially associated risk factor for sarcopenia.

| Total $n$ = 51 | | | | |
|---|---|---|---|---|
| Characteristic | B | Hazard Ratio | $CI_{95\%}$ | $p$-Value |
| Albumin (< 3.5 g/dL) | 0.153 | 1.165 | (0.552–2.46) | 0.688 |
| Barthel index (< 21) | 0.085 | 1.088 | (0.306–3.87) | 0.896 |
| BMI (> 24.9) | −1.250 | 0.287 | (0.095–0.866) | 0.027* |

CI: confidence interval.
* Statistically significant, p < 0.05.

the results. First, we did not have information about the causes of death, and the type of co-morbidities were not identified. Second, the results are based on a single rehabilitation division, therefore this sample might not represent other populations.

## 5. Conclusions

In summary, this study shows that sarcopenia is associated with low Barthel index, low BMI but higher android fat. The combination of sarcopenia and Alzheimer's disease along with other co-morbidities increases the mortality risk in sarcopenic patients. Finally, malnutrition demonstrated in low albumin levels can decrease the survival rates, whereas, BMI > 24.9 can play a positive prognostic effect on the survival as it is associated with reduced mortality hazard. These results suggest that exercise and protein supplementation are suitable interventions for preventing the development of sarcopenia in elderly adults and in reducing the mortality risk in sarcopenic patients. Cognitive therapy, memory training and mental stimulation to increase the independence of sarcopenic patients with Alzheimer's disease could improve their survival.

## Author contributions

Conceptualization, S.P. and H.A; methodology, S. P, H. A and M.A.; formal analysis, H.A.; data curation and investigation, C.G., V.I., E.C., G.P., A.R., G. P and M.R.; writing-original draft and visualization, H.A.; review and editing S.P., A.S. and M.A.; Funding acquisition; S.P., A.R. and G.P.

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## Declaration of competing interest

None.

## References


Anker, S.D., Morley, J.E., Haehling, S., 2016. Welcome to the ICD-10 code for sarcopenia. J. Cachexia. Sarcopenia Muscle 7, 512–514.

Arango-Lopera, V.E., et al., 2013. Mortality as an adverse outcome of sarcopenia. J. Nutr. Heal. Aging. 17, 259–262.

Association, A., 2015. 2015 Alzheimer's disease facts and figures. Alzheimers Dement. 11, 332–384.

Bae, E., Kim, Y., 2017. Factors affecting sarcopenia in Korean adults by age groups. Osong Public Heal. Res. Perspect. 8, 159–168.

Bae, E.J., Park, N.J., Sohn, H.S., Kim, Y.H., 2019. Handgrip strength and all-cause mortality in middle-aged and older Koreans. Int. J. Environ. Res. Public Health 16, 740. https://doi.org/10.3390/ijerph16050740.

Balogun, S., et al., 2019. Prospective associations of osteosarcopenia and osteodynapenia with incident fracture and mortality over 10 years in community-dwelling older adults. Arch. Gerontol. Geriatr. 82, 67–73.

Baumgartner, R.N., Koehler, K.M., Gallagher, D., et al., 1998. Epidemiology of sarcopenia among the elderly in New Mexico. Am. J. Epidemiol. 147, 755–763.

Beaudart, C., Zaaria, M., Pasleau, F., Reginster, J.Y., Bruyère, O., 2017. Health outcomes of sarcopenia: a systematic review and meta-analysis. PLoS One 12, 1–16.

Björkmana, M., Pitkalab, K., Jyväkorpib, S., Strandberga, T., Tilvisa, R., 2019. Bioimpedance analysis and physical functioning as mortality indicators among older sarcopenic people. Exp. Gerontol. 122, 42–46.

Bone, A., Hepgul, N., Kon, S., Maddocks, M., 2017. Sarcopenia and frailty in chronic respiratory disease: lessons from gerontology. Chron. Respir. Dis. 14, 85–99.

Bravo-Jos, P., Moreno, E., Espert, M., Romeu, M., Martínez, P., Navarro, C., 2018. Prevalence of sarcopenia and associated factors in institutionalised older adult patients. Clin. Nutr. ESPEN. 27, 113–119.

Brown, J., Harhay, M., Harhay, M., 2016. Sarcopenia and mortality among a population-based sample of community-dwelling older adults. J. Cachexia. Sarcopenia Muscle 2016 (7), 290–298. https://doi.org/10.1002/jcsm.12073.

Clark, B.C., Manini, T.M., 2010. Functional consequences of sarcopenia and dynapenia in the elderly. Curr. Opin. Clin. Nut.r Metab. Care. 13, 271–276.

Cruz-Jentoft, A.J., et al., 2019. Sarcopenia: revised European consensus on definition and diagnosis. Age Ageing 48, 16–31.

Damanti, S., Azzolino, D., Roncaglione, C., Arosio, B., Rossi, P., Cesari, M., 2019. Efficacy of nutritional interventions as stand-alone or synergistic treatments with exercise for the management of sarcopenia. Nutrients 11, 1991.

De Martinis, M., Franceschi, C., Monti, D., Ginaldi, L., 2006. Inflammation markers predicting frailty and mortality in the elderly. Exp. Mol. Pathol. 80, 219–227.

Edwards, M.H., Dennison, E.M., Aihie Sayer, A., Fielding, R., Cooper, C., 2015. Osteoporosis and sarcopenia in older age. Bone 80, 126–130.

Folstein, M.F., Folstein, S.E., McHugh, P.R., 1975. "Mini-mental state": a practical method for grading the cognitive state of patients for the clinician. J. Psychiatr. Res. 12, 189–198.

Ginaldi, L., De Martinis, M., 2016. Osteoimmunology and beyond. Curr. Med. Chem. 23, 3754–3774. https://doi.org/10.2174/0929867323666160907.

Hirschfeld, H.P., Kinsella, R., Duque, G., 2017. Osteosarcopenia: where bone, muscle, and fat collide. Osteoporos. Int. 28, 2781–2790.

Hoste, E.A., Clermont, G., Kersten, A., et al., 2006. RIFLE criteria for acute kidney injury are associated with hospital mortality in critically ill patients: a cohort analysis. Crit. Care 10, 1.

Houston, D., Nicklas, B., Ding, J., Harris, T., Tylavsky, F., Newman, A., Lee, J., Sahyoun, N., Visser, M., Kritchevsky, S., 2008. Dietary protein intake is associated with lean mass change in older, community-dwelling adults: the Health, Aging, and Body Composition (Health ABC) study. Am. J. Clin. Nutr. 87, 150–155.

Hunter, G., Singh, H., Carter, S., Bryan, D., Fisher, G., 2019. Sarcopenia and its implications for metabolic health. J. Obes. https://doi.org/10.1155/2019/8031705.

Im, I.J., Choi, H.J., Jeong, S.M., Kim, H.J., Son, J.S., Oh, H.J., 2017. The association between muscle mass deficits and arterial stiffness in middle-aged men. Nut. Metab. Cardiovasc. Dis. 27, 1130–1135.

Isanejad, M., Mursu, J., Sirola, J., Kröger, H., Rikkonen, T., Tuppurainen, M., Erkkilä1, A., 2016. Dietary protein intake is associated with better physical function and muscle strength among elderly women. Br. J. Nutr. 115, 1281–1291.

Jung Hee, K., et al., 2014. Sarcopenia: an independent predictor of mortality in community-dwelling older Korean men. J. Gerontol. A Biol. Sci. Med. Sci. 69, 1244–1252.

Kalinkovich, A., Livshits, G., 2017. Sarcopenic obesity or obese sarcopenia: a cross talk between age-associated adipose tissue and skeletal muscle inflammation as a main mechanism of the pathogenesis. Ageing Res. Rev. 35, 200–221.

Klein, B.E., Klein, R., Knudtson, M.D., Lee, K.E., 2005. Frailty, morbidity and survival. Arch. Gerontol. Geriatr. 41, 141–149.

Kortebein, P., Ferrando, A., Lombeida, J., Wolfe, R., Evans, W.J., 2007. Effect of 10 days of bed rest on skeletal muscle in healthy older adults. JAMA 297, 1772–1774.

Landi, F., Liperoti, R., Fusco, D., Mastropaolo, S., Quattrociocchi, D., Proia, A., Russo, A., Bernabei, R., Onder, G., 2012a. Prevalence and risk factors of sarcopenia among nursing home older residents. J. Gerontol. A Biol. Sci. Med. Sci. 67 A, 48–55.

Landi, F., Liperoti, R., Russo, A., et al., 2012b. Sarcopenia as a risk factor for falls in elderly individuals: results from the ilSIRENTE study. Clin. Nutr. 31, 652–658.

Landi, F., Calvani, R., Tosato, M., et al., 2016. Impact of physical function impairment and multimorbidity on mortality among community-living older persons with sarcopaenia: results from the ilSIRENTE prospective cohort study. BMJ Open 6, 1–7.

Liang, F., Chan, W., Chen, P., Zimmerman, C., Waring, S., Doody, R., 2016. Cognitively-related basic activities of daily living impairment greatly increases the risk of death in alzheimers disease. PLoS One 11, 1–11.

Liguori, I., et al., 2018. Sarcopenia: assessment of disease burden and strategies to improve outcomes. Clin. Interv. Aging 13, 913–927.

Mahoney, F., Barthel, D., 1965. Functional evaluation: the Barthel index. Maryland State Med J 14, 61–65.

Malafarina, V., Malafarina, C., Ugarte, A., Martinez, J., Goñi, I., Zulet, M., 2019. Factors associated with sarcopenia and 7-year mortality in very old patients with hip fracture admitted to rehabilitation units: a pragmatic study. Nutrients 11, 2243. https://doi.org/10.3390/nu11092243.

Mathiowetz, V., Rennells, C., Donahoe, L., 1985. Effect of elbow position on grip and key pinch strength. J Hand Surg Am 10, 694–697.

Ogawa, Y., Yoshitsugu, K., Tomohiko, S., Soichiro, S., Hidekazu, K., Haruo, H., 2018. Sarcopenia and muscle functions at various stages of alzheimer disease. Front. Neurol. 9, 1–7.

Ostrakhovitch, E.A., Tabibzadeh, S., 2019. Homocysteine and age-associated disorders. Ageing Res. Rev. 49, 144–164.

Pelegrini, A., et al., 2018. Sarcopenia: prevalence and associated factors among elderly from a Brazilian capital. Fisioter. em Mov. 31, 1–8.

Perna, S., et al., 2018. Osteosarcopenic visceral obesity and osteosarcopenic subcutaneous obesity, two new phenotypes of sarcopenia: prevalence, metabolic profile, and risk factors. J. Aging Res. 16, 6147426. https://doi.org/10.1155/2018/6147426.

Perna, S., Spadaccini, D., Rondanelli, M., 2019. Sarcopenic obesity: time to target the phenotypes. J. Cachexia. Sarcopenia Muscle 10, 710–711.

Plauth, M., Cabré, E., Riggio, O., et al., 2006. ESPEN guidelines on enteral nutrition: liver disease. Clin. Nutr. 25, 285–294.

Sieber, C.C., 2019. Malnutrition and sarcopenia. Aging Clin. Exp. Res. 31, 793–798.

Silva, B.G.C.d., et al., 2019. Associations of physical activity and sedentary time with body composition in Brazilian young adults. Sci. Rep. 9, 1–10.

Sousa, A.S., Guerra, R.S., Fonseca, I., Pichel, F., Ferreira, S., Amaral, T.F., 2016. Financial impact of sarcopenia on hospitalization costs. Eur. J. Clin. Nutr. 70, 1046–1051.

Tournadre, A., Vial, G., Capel, F., Soubrier, M., Boirie, Y., 2019. Sarcopenia. Joint Bone Spine 86, 309–315.

Vasan, R.S., Levy, D., 2000. Defining diastolic heart failure a call for standardized diagnostic criteria. Circulation 101, 2118–2121.

Vetrano, D., Landi, F., Volpato, S., Corsonello, A., Meloni, E., Bernabei, R., Onder, G., 2014. Association of sarcopenia with short- and long-term mortality in older adults admitted to acute care wards: results from the CRIME study. J. Gerontol. A Biol. Sci. Med. Sci. 69, 1154–1161.

Wall, B., Dirks, M., Snijders, T., Senden, J., Dolman, J., Vaan Loon, L., 2014. Substantial skeletal muscle loss occurs during only 5 days of disuse. Acta Physiol (Oxf) 210, 600–611.

Welchl, C., Hassan-Smith, Z., Greig, C., Lord, J., Jackson, T., 2018. Acute sarcopenia secondary to hospitalisation - an emerging condition affecting older adults. Aging Dis. 2018 (9), 151–164.

Yanjiao, S., et al., 2019. Prevalence and associated factors of sarcopenia in nursing home residents: a systematic review and meta-analysis. J. Am. Med. Dir. Assoc. 20, 5–13.

Zhang, Z., Pereira, S.L., Luo, M., Matheson, E.M., 2017. Evaluation of blood biomarkers associated with risk of malnutrition in older adults: a systematic review and meta-analysis. Nutrients 9, 829. https://doi.org/10.3390/nu9080829.

Zhang, X., Wang, C., Dou, Q., Zhang, W., Yang, Y., Xie, X., 2018. Sarcopenia as a predictor of all-cause mortality among older nursing home residents: a systematic review and metaanalysis. BMJ. https://doi.org/10.1136/bmjopen-2017-021252.