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Impact of sarcopenia on 1-year mortality in older patients with cancer

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Abstract

Objectives: sarcopenia is common especially in hospitalised older populations. The aim of this study was to assess the prevalence of sarcopenia, defined as low skeletal mass and muscle strength, and its impact on 1-year mortality in older patients with cancer.

Methods: skeletal muscle mass was estimated using bioelectric impedance analysis and related to height^2 (SMI; Janssen *et al*. 2002). Grip strength was measured with the JAMAR dynamometer and the cut-offs suggested by the European

Working Group on Sarcopenia in Older People (EWGSOP) were applied. One-year mortality was assessed by telephone follow-up and the local cancer death registry.

Results: of the 439 consecutively recruited cancer patients (60–95 years; 43.5% women), 119 (27.1%) had sarcopenia. Of the patients with sarcopenia, 62 (52.5%) died within 1 year after study entry compared to 108 (35.1%) patients who did not have sarcopenia ($P = 0.001$). In a stepwise, forward Cox proportional hazards analysis, sarcopenia (HR = 1.53; 95% CI: 1.034–2.250; $P < 0.05$), advanced disease (HR = 1.87; 95% CI: 1.228–2.847; $P < 0.05$), number of drugs/day (HR = 1.11; 95% CI: 1.057–1.170; $P < 0.001$), tumour diagnosis (overall $P < 0.05$) and Karnofsky index (HR = 0.98, 95% CI: 0.963–0.995; $P < 0.05$) associated with 1-year mortality risk. The factors sex, age, co-morbidities and involuntary 6-month weight loss ≥5% were insignificant.

Conclusions: sarcopenia was present in 27.1% of older patients with cancer and was independently associated with 1-year mortality. The fact that sarcopenia was nearly as predictive for 1-year mortality as an advanced disease stage underlines the importance of preservation of muscle mass and function as a potential target of intervention in older patients with cancer.

Keywords

sarcopenia, mortality, cancer, old, advanced disease, older people

Key points

- Sarcopenia was prevalent in 27.1% of old patients with cancer.
- Sarcopenia was nearly as predictive for 1-year mortality as an advanced disease stage.
- Preservation of muscle mass and function should be a target of intervention in older patients with cancer.

Introduction

Sarcopenia, the progressive degeneration of muscle mass [1], has become a well-known condition in older adults. Numerous studies have described risk factors such as sex [2, 3] and inflammatory disease [4] in addition to age. The negative clinical outcomes associated with sarcopenia are well established. Impaired functional independence [5] and quality of life as a result of reduced muscle mass and strength culminate in increased morbidity and mortality [3, 6–8]. Consequently, low muscle mass or sarcopenia is associated with increased direct and indirect health care costs [9]. A single operational definition and diagnostic criteria of sarcopenia, however, are still under discussion; thus, making the comparison of study results, i.e. prevalence data, difficult. The European Working Group on Sarcopenia in Older People (EWGSOP) published a consensus definition in 2010 including low muscle mass and muscle strength with corresponding cut-off values [10]. Using this definition, a systematic review reported a prevalence of 1–29% in older, community-dwelling populations (≥50 years) [11]. Smoliner *et al.* [12] reported a prevalence of approximately 25% using this definition in hospitalised, geriatric patients in Germany.

Cancer patients are subjected to a number of factors that can influence muscle mass, including anorexia and reduced physical activity, surgery, chemotherapy, radiotherapy or hormonal therapy [13, 14]. Conversely, sarcopenia in cancer patients clearly has a negative impact on therapy tolerance, including an increased risk of chemotherapy toxicity [15], postoperative complications [16] and mortality risk [17]. Recently, a prevalence of 15% was reported for sarcopenia in adults with colorectal cancer (35% of study population ≥65 years [18]) and 21.2% in older patients with gastric cancer based on the EWSGOP criteria [16]. In the following study, we analysed clinical features and sarcopenia according to the EWSGOP criteria in a population of older patients with mixed cancer types in inpatient care and the impact of sarcopenia on 1-year mortality.

Methods

Study population

This study was a post hoc analysis of a prospective observational study in old cancer patients, registered at clinicaltrials.gov as NCT01120483. Patient recruitment was carried out from January 2006 to December 2007 and from March 2010 to July 2011. Within this time, patients admitted to the Charité University hospital for cancer treatment or staging were consecutively included. Inclusion criteria was diagnosis of solid or haematologic tumour disease of any type or stage. Patients were not eligible for study inclusion if currently included in intervention or drug trials. Also, patients with implanted pacemakers or defibrillators as well as patients with neuromuscular degenerative disease, hemiplegia or severe arthritis in the extremities were excluded to avoid potential confounders on muscle mass and strength. Additionally, patients with cognitive impairments according

to neuropsychological tests or as judged by the study investigators during the patient briefing or patients who could not speak or understand the German language were excluded. All patients gave written informed consent. The study was approved by the corresponding ethics committee, Ethic's Committee of the Charité University Medicine, Berlin, Germany. For this analysis, only patients aged 60 and above were included.

Demographic characteristics and clinical data including age, sex, co-morbidities and medication as well as date of tumour diagnosis, tumour location and stage according to the UICC (Union Internationale Contre le Cancer; stages I–IV (advanced)) classification, disease duration and type of treatment were documented. The Karnofsky Performance Index (KI), which classifies patients on a scale of 0–100 according to well-being, symptoms and functional impairment in activities of daily life, was determined. Values under 50 indicate pronounced impairment and symptoms with the need for medical care, low self-care and hospitalisation.

All measurements were performed within 48 h of hospital admission.

Information on mortality within one year of study enrolment was collected by a telephone follow-up and by contacting the local cancer death registry.

Anthropometric measurements and body composition analysis

Weight was measured in light clothing and without shoes with a portable electronic scale (seca 910, max. 200 kg ± 100 g, seca GmbH, Hamburg, Germany) to the nearest 0.1 kg. Height was measured with a portable stadiometer (seca 220 telescopic measuring rod, seca GmbH, range: 60–200 cm) without shoes to the nearest 0.1 cm. Weight and height were used to calculate body mass index (BMI) as weight (kg)/height $(m)^2$. Patients reported on changes in body weight in the previous 6 months.

Bioelectric impedance analysis (BIA) was performed under standard conditions with a Nutriguard M (Data-Input GmbH, Darmstadt, Germany) applying an alternating current of 800 µA at 50 kHz. The tetrapolar approach was applied with electrodes (Ag/AgCl, Bianostic AT, Data-Input GmbH) placed on the dorsal side of the hand and foot on the dominant side of the body. Patients were measured in the morning after an overnight fast in the supine position with the arms and legs abducted from the body. Using physical (height and weight) and impedance (R and Xc) parameters, skeletal muscle mass (SM) was calculated with the equation by Janssen *et al.* [19]. Skeletal muscle mass index (SMI) was calculated by dividing SM by the square of height.

Muscle strength

Isometric hand grip strength was measured with a JAMAR® dynamometer (Sammons Preston Roylan, Bolingbrook, Illinois) in the non-dominant hand. The test was performed in a seated position with the shoulder adducted and neutrally rotated, the elbow flexed to 90°, forearm and wrist in a neutral position. The patients performed a maximum isometric contraction three times with approximately 30 s between repetitions. The highest value was documented.

Sarcopenia

Sarcopenia was defined according to the suggestion by EWGSOP as low SMI and low hand grip strength [10]. The cut-offs for SMI were $<10.75\ kg/m^2$ for men and $<6.75\ kg/m^2$ for women, based on a reference group of men and women over 60 years of age [20]. The cut-offs for hand grip strength were sex- and BMI-stratified and consistent with the cut-off values used for hand grip strength in the characterisation of frailty [21].

Statistics

Data analysis was performed using the statistics program IBM SPSS Statistics Version 23. Age, body composition and strength variables as well as KI, number of drugs and co-morbidities were described by means and standard deviations and treated as continuous variables in the analyses. The presence of sarcopenia, tumour stage and diagnosis category were described as nominal variables and presented as percent values.

Comparisons between patients with and without sarcopenia were conducted with a Student's *t*-test for continuous variables or the chi-squared test for nominal variables.

A forward, stepwise Cox proportional hazards regression was conducted to assess risk factors of 1-year mortality. Survival time was calculated as number of days from study baseline to 1-year follow-up. Data from patients who were alive after 1 year were censored. Factors included sex (men versus women), age, number of co-morbidities and drugs per day, KI, weight loss ≥5% within the previous 6 months (yes versus no), tumour stage (IV versus I–III), tumour category (compared to gastrointestinal tumours) and sarcopenia (yes versus no).

Kaplan–Meier 1-year survival curves were generated for patients with and without sarcopenia and the log-rank test carried out to test for differences in survival distributions.

For all tests, a significance level of less than 5% was chosen a priori.

Results

Overall, 439 patients from 60 to 95 years were included in the study (43.5% women). Gastrointestinal tumours were the most common, followed by haematologic and urogenital tumours. And 149 (32.1%) presented with tumour stages I to III, while 260 (64.8%) had advanced disease stage IV (Table 1).

A total of 297 (67.7%) and 186 (42.4%) were below the cut-off values for SMI and hand grip strength, respectively. And 119 (27.1%) had both low SMI and hand grip strength,

Table 1. Characteristics of study population.

	All (n = 439)	Sarcopenia (n = 119)	No sarcopenia (n = 320)	P-value
Sex (male)	248 (56.5%)	82 (68.9)	166 (51.9)	0.001
Age (years)	69.6 ± 6.2 (60.0–95.4)	71.7 ± 6.7	68.8 ± 5.8	<0.001
BMI (kg/m^2)	25.0 ± 4.7 (15.2–51.4)	23.3 ± 3.7	25.6 ± 4.9	<0.001
SMI (kg/m^2)	8.5 ± 1.8 (4.5–13.9)	8.0 ± 1.8	8.7 ± 1.8	0.001
Hand grip strength (kg)	25.9 ± 9.4 (1.0–54.0)	20.2 ± 6.6	28.0 ± 9.5	<0.001
Karnofsky index (%)	73.8 ± 12.1 (20–100)	68.3 ± 12.5	75.9 ± 11.3	<0.001
Number of drugs/day	5.5 ± 3.8 (0–19)	6.7 ± 4.2	5.1 ± 3.5	<0.001
Number of co-morbidities	3.8 ± 2.4 (0–12)	4.4 ± 2.4	3.6 ± 2.3	0.001
Disease duration (months)[a]	25.0 ± 40.7	20.1 ± 30.8	26.8 ± 43.8	0.080
Advanced tumour stage IV	260 (64.8)	69 (63.9)	191 (65.2)	0.809
Treatment type				
Chemotherapy	246 (56.0)	64 (55.7)	182 (58.0)	
Radiation therapy	34 (7.7)	11 (9.6)	23 (7.3)	0.876
Other	24 (5.5)	7 (6.1)	17 (5.4)	
No treatment	125 (28.5)	33 (28.7)	92 (29.3)	

Data are presented as mean ± SD (min. – max.) and Student's t-test or mean (%) and chi-squared test to compare groups. BMI, body mass index; Karnofsky index, 0–100; SMI, skeletal muscle mass index.
[a]Duration refers to date of first diagnosis to study inclusion.

Table 2. Sarcopenia as a predictor of 1-year mortality in a forward, stepwise Cox proportional hazards regression.

	HR	95% CI		P value
Sarcopenia	1.53	1.034	2.250	0.033
Advanced tumour stage IV	1.87	1.228	2.847	0.004
Number of drugs/day	1.11	1.057	1.170	<0.001
Karnofsky Index	0.98	0.963	0.995	0.013
Diagnosis category[a]				0.012
Oropharynx	0.517	0.236	1.134	0.100
Urogenital	0.660	0.377	1.156	0.146
Haematologic	0.386	0.175	0.851	0.018
Other	1.762	0.938	3.310	0.078
Lung	0.913	0.469	1.682	0.770

CI, confidence interval; HR, hazard ratio. The following parameters were included in the analysis: sex, age, number drugs per day and co-morbidities, KI, weight loss ≥5% within previous 6 months (yes versus no), tumour stage (IV versus I–III), tumour diagnosis category and sarcopenia (yes versus no).
[a]Reference variable: gastrointestinal tumours.

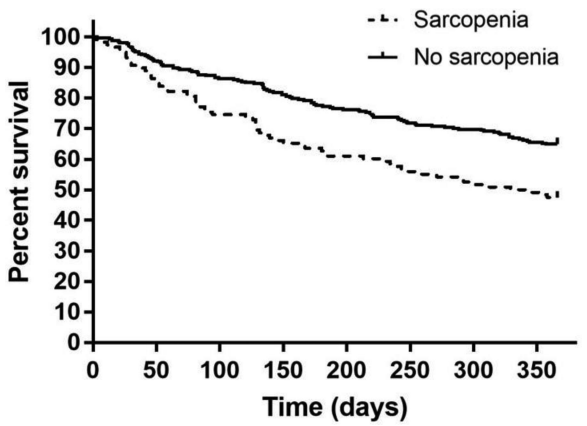

Figure 1 Kaplan–Meier 1-year survival curves for patients with (dashed line) and without sarcopenia (black line).

corresponding to sarcopenia. In addition to low SMI and hand grip strength, patients with sarcopenia were more often male, were older, had lower BMI and KI as well as more drugs per day and co-morbidities (Table 1). Tumour type did not differ significantly between patients with and without sarcopenia (P = 0.183, data not shown). Disease duration from the time of first diagnosis to study inclusion was somewhat longer in patients without sarcopenia but did not differ significantly (Table 1). Of the patients with sarcopenia, 63.9% presented with advanced disease (Table 1). Most patients (69.2%) were receiving active cancer treatment, of which, chemotherapy was the most common. The remaining patients were not or no longer receiving treatment for the active disease at the time of study inclusion. Type of treatment did not differ between patients with and without sarcopenia (Table 1).

Body weight loss in the previous 6 months was more common in patients with sarcopenia (with versus without sarcopenia: 81.3 versus 65.9%, $P < 0.05$) and patients with sarcopenia lost more weight than those without (11.3 ± 7.0% versus 9.2 ± 5.8%, $P < 0.05$).

Death was confirmed for 241 (54.9%) patients, 170 of which (38.7%) died within 1 year of study entry. One-year mortality was significantly different between tumour diagnoses. While gastrointestinal tumours were the most common in this study population, more patients died within 1 year of study entry proportionally in the urogenital (46.2%), lung (51.5%) and other (68.2%) tumour diagnosis groups (versus 40.3% of gastrointestinal tumour patients; P = 0.004). In total, 62 (52.5%) patients with sarcopenia died within 1 year of study entry compared to 108 (35.1%) patients who did not have sarcopenia (P = 0.001).

In the stepwise Cox proportional hazards regression analysis, sarcopenia along with number of drugs per day, KI, advanced disease and tumour diagnosis category were significant predictors of 1-year mortality (Table 2).

Figure 1 shows the Kaplan–Meier survival curves. The mean survival time was longer in patients without

sarcopenia (291.2 days; 95% CI: 278.0–304.5 versus 244.0 days; 95% CI: 219.2–268.7) and the survival distributions differed significantly between patients with and without sarcopenia ($X^2 = 12.879$, $P < 0.001$).

Discussion

In this study of older individuals over 60 years of age with different cancer types, we found a prevalence of sarcopenia according to the definition proposed by EWGSOP of 27.1%. Patients with sarcopenia were older, had a lower BMI, had experienced higher weight loss, reported lower functional performance as well as more co-morbidities and medication. Furthermore, the presence of sarcopenia emerged as a strong predictor of 1-year mortality, nearly as strong as advanced tumour stage.

During the revision of this article, a revised EWGSOP consensus definition for sarcopenia was published and recommends hand grip strength as the hallmark criteria in the identification of sarcopenia. Of particular note at this point is that the prevalence of sarcopenia in our study population remained the same when only considering hand grip strength and the proposed cut-off values in EWGSOP2 [22]. Nevertheless, the original EWGSOP definition of sarcopenia is the basis of this discussion.

The prevalence of sarcopenia in older patients with cancer is comparable to that in a mixed, older, hospitalised population according to the EWGSOP definition. Smoliner *et al.* [12] reported a prevalence of 25% in a hospitalised, geriatric population in Germany, in which merely 6.1% of the nearly 200 study participants were diagnosed with a tumour disease. Martone *et al.* [23] recently reported a higher prevalence of 34.7% in older patients at hospital admission (12.9% with cancer; geriatric and internal medicine acute care wards) in an Italian multicenter study also using the EWGSOP definition. Additionally, they found that 14.7% of patients developed sarcopenia during hospital stay. In comparison, a large systematic review and meta-analysis recently reported a worldwide prevalence of 10% in healthy adults over 60 years old [24]. The higher prevalence of sarcopenia in hospitalised older patients most probably reflects the negative impact of inactivity and chronic disease on muscle in addition to the physiological and hormonal changes related to ageing [4]. Many patients are likely additionally affected by cachexia, which exacerbates sarcopenia and may explain why so many patients had low SMI in our study. While age-related sarcopenia is described as the loss of skeletal muscle due to physiological and hormonal changes occurring in ageing [4], cachexia refers to a complex syndrome characterised by systemic inflammation and abnormal metabolism with loss of muscle mass with or without loss of fat mass as well as reduced food intake [4, 25]. Therefore, diagnostic criteria suggested for cancer cachexia include significant weight loss, low BMI and low SMI [26]. Consequently, patients with cachexia are often also sarcopenic [10] and older patients with cancer are confronted with a double blow on muscle tissue maintenance. Not only the loss of tissue mass but also the loss of cell integrity, represented by low bioelectrical phase angle, in older patients with cancer has previously been shown to be predictive of negative clinical outcome [27].

Considerably more patients had low SMI than low hand grip strength. The prevalence of patients with just low muscle mass (67.7%) was comparable to that reported by other studies in cancer. Broughman *et al.* [28] showed low SMI in 56–60% of old patients with colorectal cancer using muscle cross-sectional area obtained by CT. While patients in our analysis were characterised using the diagnostic criteria of age-related sarcopenia, it is difficult and perhaps not possible to disentangle effects of age-related sarcopenia and cancer-cachexia in this population. This disadvantage has also been stated by Muscaritoli *et al.* [26] in the consensus definition of sarcopenia, cachexia and pre-cachexia. Knowing the etiology of low muscle mass may, however, help to determine optimum therapy in sarcopenic patients.

Few previous studies have analysed mortality risk in older patients with cancer and sarcopenia using a consensus definition. Huang *et al.* [29] found that the presence of sarcopenia (as defined by EWGSOP and the Asian Working Group for Sarcopenia (AWGS)) in older patients (≥65 years) with gastric cancer who underwent gastrectomy was an independent risk factor for 1-year mortality. Kawamura *et al.* [30] also investigated the influence of sarcopenia (as defined by AWGS) in older patients (≥65 years) with gastric cancer who underwent surgery. Median follow-up time was approximately 5.5 years and they found that sarcopenia was an independent predictor of overall as well as cause-specific survival in this patient group.

Considering the adverse effects of sarcopenia on outcome in older cancer patients, it is imperative to identify and monitor at-risk patients and plan or adjust therapy accordingly, not only cancer-specific but also nutritional and physical therapy, in order to improve patients' prognosis.

Our study is subject to limitations. We did not have information on cause of death and it was impossible to distinguish between cancer cachexia and age-related sarcopenia and therefore their contribution to mortality.

In summary, the present data suggest that in older patients with cancer, sarcopenia defined using simple beside measures such as BIA-derived SMI and hand grip strength is prevalent and significantly associated with increased 1-year mortality.

This phenotype in these patients was nearly as predictive for 1-year mortality as an advanced disease stage; thus, underlining the necessity of continued assessment of muscle mass and strength and its preservation as a potential target of intervention in older patients with cancer.

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Novartis Company, personal fees from Bayer Company, outside the submitted work. Dr Norman reports honoraria for independent lectures on the relevance of body composition/loss of muscle mass.

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