Cancer-related fatigue: the impact of skeletal muscle mass and strength in patients with advanced cancer

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Running title: Cancer-related fatigue is related to muscle mass and strength

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Abstract

Background Although exertional fatigue is directly and negatively related to skeletal muscle mass and strength, it is currently unknown if these variables are associated with cancer-related fatigue (CRF). Therefore, the purpose of this study was to determine if CRF is associated with measures of appendicular lean muscle mass and strength in advanced cancer patients (ACP).

Methods and results Eighty-four patients (48 men, 36 women aged 61.6 ±13.2 yrs) newly-diagnosed (≤6 months) with inoperable (Stages III-IV) gastrointestinal or non-small cell lung cancer participated in this study. All patients completed the Brief Fatigue Inventory (BFI). Handgrip (HGS) and quadriceps (QS) strength were assessed using isometric and isokinetic dynamometry, respectively. Skeletal muscle mass index (SMMI) was calculated from the appendicular lean mass measured via dual-energy X-ray absorptiometry divided by body height squared. Univariate analysis showed BFI to be significantly associated with body mass index, weight loss, anemia, hypoalbuminemia, activity level, depression, and sarcopenia along with SMMI, HGS, and QS. HGS ($r = -0.34$; $p=0.018$), QS ($r = -0.39$; $p=0.024$) and SMMI ($r = -0.60$; $p<0.001$) were negatively correlated with BFI total scores in men but not in women. When adjusted for sex, age, diagnosis, survival, along with the above characteristics, multivariate analyses showed that BFI scores were negatively associated with HGS (B:-0.90; 95%CI -1.5:-0.3), QS (-0.2; -0.3:-0.01), and SMMI (-7.5; -13.0:-2.0). There was a significant sex x SMMI interaction (10.8; 1.2: 20.5), where BFI decreased with increasing SMMI in men, but did not change with SMMI in women. *Conclusion* These results suggest that in ACP, CRF

is related to muscle mass and strength, which may provide a target for future intervention.

Keywords Fatigue, Cancer, Skeletal muscle mass index, Strength

Introduction

Cancer-related fatigue (CRF) is a highly prevalent and multi-factorial symptom that is classically defined as “a persistent, subjective sense of tiredness related to cancer or cancer treatment that interferes with usual functioning” [1]. Although the specific etiology of CRF remains largely unknown, it is frequently associated with a wide variety of psychosocial factors (e.g., clinical depression, anxiety, and coping with chronic illness), and exacerbating symptoms (e.g., chronic pain, dyspnea, insomnia, nausea, and weight loss) [2,3] as well as antineoplastic treatment side effects (chemotherapy, radiotherapy, surgery, and medications) [4]. In addition, several co-morbid medical conditions and biomarkers have been correlated with fatigue including anemia [5], hypoalbuminemia [6], elevated levels of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and IL-6 [7]. Many of these factors are inextricably linked to one another in promoting fatigue. For example, TNF-α and IL-6 have been shown to inhibit erythropoiesis resulting in anemia and fatigue. Thus, it is not surprising that treatment with epoietin-α has demonstrated positive results in alleviating CRF [8] Hypogonadism (low serum testosterone) is also associated with CRF [9]. In fact, not only is low concentration of testosterone a major contributor of fatigue but it has been included in a list of biomarkers responsible for cachexia-related weight loss and muscle wasting [10].

Considering what is known about cancer cachexia and fatigue, it is surprising that a strong relationship between CRF and muscle mass/strength has yet to be established. Cancer-related fatigue has been directly related to mid-arm circumference [11,12] and

skin-fold measurements [13], but these assessment techniques can only provide a gross estimate of the two compartments comprising forearm muscle mass and subcutaneous fat. A more precise and accurate method of assessment must be done in order to determine the composition of the specific limb compartments (e.g., lean body mass / fat mass). Once the appendicular lean mass is determined, then more definitive statements can be made regarding the relationship between mass and strength and their impact on the severity of CRF.

What is the importance of establishing these relationships? With the advent of novel CRF models linking behavioural and physiological indices, a reduction in muscle mass coupled with muscle weakness could be the objective measures that partially explain the degree of tiredness and exhaustion experienced by many patients with advanced cancer [14]. There is a definite link between muscle mass/strength and fatigue. For instance, various types of physical activity programs known to improve physical conditioning, muscle mass, and strength have proven to be beneficial in relieving CRF. There is evidence for the benefit of aerobic activity [15, 16] and resistance training [17] in reducing CRF. Conversely, de-conditioning as a result of prolonged bedrest reduces muscle mass and strength and leads to chronic fatigue [18]. Whether muscle mass and strength directly affect fatigue or they are simply a consequence of the condition that is causing the fatigue remains to be clarified.

Identifying the potential clinical significance of progressive declines in both upper and lower skeletal muscle mass and strength is of vital importance especially in fatigued patients suffering from cancer cachexia [19]. Thus, there is a growing need to design

studies that specifically address whether an independent relationship exists between CRF and muscle strength as well as skeletal muscle mass, while at the same time adjusting for relevant confounding covariates. To date, we are not aware of any published report identifying an association between CRF and measures of overall body strength and the respective skeletal muscle limb masses in a cohort of advanced cancer patients. Therefore, the purpose of this study was to determine whether or not CRF is related to specific objective measures of appendicular muscle mass (e.g., skeletal muscle mass index (SMMI)) as well as upper and lower body muscle strength in patients with advanced gastrointestinal and non-small cell lung cancers.

Methods

Patient recruitment

All patients were assessed within 6 months of being diagnosed with inoperable (Stages III-IV) gastrointestinal (GI) or non-small cell lung cancer (NSCLC) and recruited between March and November 2007 from the McGill University Health Center (MUHC). All the assessments (e.g., body composition, upper and lower body strength, and BFI) took place at the McGill Nutrition and Performance Laboratory (MNUPAL). Ethical approval was obtained from the Institutional Review Board of McGill University. Informed consent was obtained in writing from all subjects prior to recruitment. All data was stored in the MNUPAL Human Cancer Cachexia Database (HCCD).

Selection of patients and measures from the HCCD

Of the 210 patients in the HCCD available at the time of analysis, 84 patients (48 men and 36 women) satisfied the selection criteria for this study. The selection criteria included having a DXA scan, assessments for isometric strength of the forearm using handgrip dynamometry, isokinetic dynamometry of the quadriceps extensors using the BIODEX, and the completion of the Brief Fatigue Inventory. No exclusion of patients were made on the base of their comorbidities or concurrent medications, but the information about these two characteristics was accounted for in our analyses (see below)

All study patients were evaluated for appendicular lean mass (ALM) using DXA (Lunar Prodigy Advance^{TM} GE Healthcare, Madison, WI, USA). Subjects were instructed to fast for 12 hours prior to their appointment at MNUPAL and avoid wearing any metal items on the day of the scan. Any patient with a pacemaker was excluded from this study. The total body DXA scan was performed with the subject positioned in the center of the DXA table, arms and legs fully extended. All subjects were instructed to remain still throughout the 6-minute scan. The DXA scans were analyzed using Advance's enCORE^{TM} 2006 software (GE Healthcare, Madison, WI, USA). The same technician manually adjusted the separation of regional appendicular body segments (e.g., arms and legs) for each scan. Using the skeleton as the reference, the arms were cut at the glenohumoral joint and the legs were cut at the neck of the femur. The software then automatically calculated the appendicular lean mass (ALM) in kilograms. This method of determining ALM conforms to that used by Heymsfield et al [20]. The skeletal muscle mass index (SMMI) was calculated by dividing ALM by the height squared (ALM/ht^2).

For isometric handgrip dynamometry, a spring-loaded, handgrip dynamometer (Jamar®, Sammons Preston, Bolingbrook, IL, USA) was used to determine isometric force of the forearm. The grip of the dynamometer was adjusted to the most comfortable position prior to collecting data on each patient. With the patient in a seated position, the dominant arm was flexed at a 90^{o} angle with the wrist as close to 0^{o} as possible. The non-dominant arm rested beside the body. Isometric handgrip force was measured 3 times in succession without rest, with each trial lasting approximately three seconds. A 3-s isometric contraction was selected since it was found that peak output could be obtained during this time without causing adverse side effects. The mean of three trials was calculated and averaged for each patient. The patient was given clear instructions when to start and stop the contraction, and was encouraged during the test to squeeze the handgrip as hard as possible. The use of the spring-loaded dynamometer to measure handgrip force has been shown to be valid and highly reliable [21] and has been used in our laboratory [22] and others [23,24] to measure handgrip strength in cancer patients.

The leg extensor strength of the quadriceps muscle group was assessed using isokinetic dynamometry (BIODEX System 3, BIODEX Medical Systems, Shirley, NY, USA). The subjects were seated in the BIODEX chair at an incline between 80 and 90°. Stabilizing straps were placed across the shoulders and hips. The BIODEX chair was adjusted until the rotational axis of the knee joint was aligned with the rotational axis of the BIODEX leg attachment at the level of the lateral epicondyle of the femur. The leg was then firmly secured to the extension attachment slightly above the ankle joint. Range of motion was determined by having the subject extend their leg as high as

possible without experiencing any discomfort (maximum extension level) and then lowering their leg to approximately 90° of flexion (maximum flexion level). The subjects were permitted to use the handlebars on either side of the BIODEX chair for additional stability during testing. Prior to the start of the test, each subject was instructed on the protocol and given a reminder that they may stop the test at any time for any reason. The protocol consisted of two sets of 5 repetitions at an angular velocity of 60°/second with a 60 s rest period between sets. Prior to the first set, 1-2 practice repetitions were performed at the pre-determined testing velocity. Subjects were instructed to perform the repetitions as fast as possible, and to begin when they were ready. During the test, the instructor counted down the number of repetitions and constantly encouraged the patient to move as fast as possible. During the rest interval between sets, the subjects fully extended and then flexed their leg in order to re-confirm the original, pre-set range of motion. The greatest peak torque value obtained from the 5 repetitions of both sets was recorded, averaged, and expressed in Newton-meters (Nm). The use of isokinetic dynamometers to evaluate strength of the knee extensors (e.g., quadriceps) has been shown to be valid and reliable [25] and has been used previously in our laboratory [21] and others [26,27] to obtain lower limb strength measures in patients with advanced cancer.

In the present study, the BFI was used to assess the severity of subjective fatigue [28]. This single page questionnaire consists of 9 items, with each item having a numerical rating between 0-10, and a 9-item global score is calculated. Three items define the severity of fatigue during normal waking hours using single word descriptors, while the 6 other items evaluate fatigue interference or how fatigue has impaired the patient's life

over the previous 24 hours. Construct validity for the 9 items ranged from 0.81 (usual fatigue) to 0.92 (activity) indicating that all 9 items are representative of a single fatigue factor [28] The concurrent validity demonstrated that BFI was significantly and strongly correlated with the Functional Assessment of Cancer Therapy-Fatigue (FACT-F) and the Profile of Mood States-Fatigue (POMS-F) subscales. Cronbach's coefficient alphas showed high reliability ($\alpha > 0.95$) and consistency with minimal measurement error for all 9 items [28]. The BFI is considered to be an acceptable subjective tool in the measurement of cancer-related fatigue and it has been validated in other languages for its use worldwide [16, 29].

Selection of covariates

The correlation between CRF and muscle mass/strength was adjusted for the following variables: cancer type and stage, prognosis, concurrent oncological treatments and medications, laboratory parameters, presence and severity of particular symptoms such as pain and depression, performance status, presence of comorbidities, along with information on isometric handgrip dynamometry, isokinetic dynamometry of the knee extensors and on appendicular lean mass. These variables were selected because they have been found to be predictive for CRF in patients with advanced cancer and were available in the HCCD [30]

For oncological treatments, we considered the presence or absence of concurrent chemotherapy and/or radiotherapy. For medications potentially impacting on fatigue, we have considered the presence or absence of at least one of the following medications: statins, anti-inflammatories (both steroidal and non-steroidal), ACE-inihibitors, anti-

hormonal agents, anti-oxidants, essential amino acids, anabolic hormones and metformin. Patient's prognosis was classified according to the presence/absence of death within 8 weeks from the time of assessment. For laboratory values, we have examined the presence or absence of high CRP (> 5g/dL), anemia (< 12 g/dL) and hypoalbuminemia (< 3.2 g/dL), as recommended by Evans et al. (10). The presence and severity of symptoms experienced at the time of patient enrollment were measured by the Edmonton Symptom Assessment Scale (ESAS) [31]. The ESAS consists of 9 visual analog scales for measuring pain, shortness of breath, nausea, depression, activity, anxiety, well-being, drowsiness, and appetite. Concurrent diseases, were measured using the Charlson comorbidity score [32]. This score ranges from 0 to a maximum of 33 and is based on the presence of certain diseases with assigned values or weights. We developed an adjusted Charlson score, which excluded the diagnosis of cancer, since our intention was to measure conditions other than the patient's principal diagnosis. Performance status was measured according to the Eastern Co-operative Oncology Group (ECOG) scale [33]. Variables were examined in the continuous and categorical form. The cutoff points for the latter were chosen according to Evans et al. (10), as well as distribution of cases, clinical meaningfulness and biologic plausibility.

Statistical analysis

Both univariate and multivariate linear regression analyses were used to test the relationships between the following variables: 1) handgrip strength (HGS), 2) quadriceps strength (QS) and 3) skeletal muscle mass index (SMMI), and BFI (dependent variable). Multivariate models were implemented in three stages. First, we created three separate linear regression models where the relationships between BFI

and HGS, QS and SMMI respectively were adjusted for age, sex, type of cancer and prognosis. Next, all independent variables selected from the HCCD were added one at a time, to the latter models to detect any significant contribution. Finally, any interaction terms among the best set of variables identified were also tested in the final three models.

All statistical analyses were performed using SPSS (version 14.0, Chicago, USA).

Results

A total of eighty-four patients [48 men and 36 women] with a mean age (SD) of 61.6 (±13.2) yrs were selected retrospectively for this study (Tables 1 & 2). Patients with metastatic gastrointestinal malignancies were more prevalent in the study sample. However, their performance status was generally fair, they had low comorbidity burden and generally they were not undergoing concurrent oncological treatments. Over a third of the sample however was on at least one medication potentially impacting on CRF. Univariate linear regression analysis showed BFI to be significantly associated with body mass index, weight loss, anemia, hypoalbuminemia, activity level, depression, and sarcopenia along with SMMI, HGS, and QS (Tables 1 & 2). There were no correlations between muscle quality and fatigue (Table 2).

HGS ($r = -0.34$; $p=0.018$), QS ($r = -0.39$; $p=0.024$) and SMMI ($r = -0.60$; $p<0.001$) were negatively correlated with BFI total scores in men but not in women (Figures 1-3). Multivariate linear regression analyses revealed that HGS (Table 3, model 1), QS (Table 4, model 1), and SMMI (Table 5, model 1) were negatively correlated with BFI. There was a significant interaction between SMMI and sex (Table 5) indicating that BFI

decreased with increasing SMMI in men, but that BFI did not change with SMMI in women (Figure 3). There were no interactions between sex and HGS (Table 3) or QS (Table 4).

Age, diagnosis, (lung vs gastrointestinal tumor) and prognosis had no significant impact on CRF, whereas pain, depression, malnutrition and concurrent chemotherapy did in most multivariate models. Performance status could not be included in the multivariate models because of collinearity issues.

Discussion

In the present study, we found that lower levels of HGS and QS, were independently associated with higher levels of CRF in patients with advanced gastrointestinal and non-small cell lung cancers while adjusting for other independent predictors of CRF in this patient population. We identified both upper and lower body muscle strength as significant predictors of CRF. Similar correlations between isometric handgrip strength and fatigue have been observed with some [11,13] but not all [12,23] cancer diagnoses. An explanation for this apparent lack of consistency as a result of multivariate regression analyses may be due to the fact that handgrip strength exerts a minimal role with increasing levels of fatigue severity [23]. The relation between lower limb strength development and fatigue has received very little attention. To date, two studies have assessed quadriceps leg strength directly in cancer patients [26,27]; however, neither study incorporated any subjective fatigue measure. Although there appears to be a paucity of published reports investigating the relationship between direct measures of leg strength and fatigue in different cancer populations, there have been reports showing a significant association between cancer-related fatigue and the 30-s timed sit-

to-stand test [13,23]. This functional test is considered to be an indirect but reliable performance measure of combined leg strength and endurance. Considering the obvious contribution of the quadriceps muscle group to the wide variety of subjective tests (e.g., sit-to-stand test, timed up and go, and the 6 minute walk test) used to assess functional performance in the cancer patient, there clearly is a need to determine the role and importance of lower limb strength as an independent variable in this relationship.

With respect to SMMI, we did observe a significant univariate correlation with CRF. However, when we controlled for our covariates, an interesting interaction emerged between SMMI and sex and BFI scores. The BFI scores were lower in males with higher SMMI while no similar relationship existed in females. Thus, it would appear the results of this study indicate that changes in muscle mass in the group of female patients are not directly related to changes in CRF. To unequivocally state that there is a true sex difference may be somewhat premature. It is conceivable that due to the limited sample size in the female group has hindered our prediction that muscle mass and fatigue are not related. Furthermore, the fact that the overall clustering of values for muscularity in men (e.g., 5.5-10.5 kg SMMI) versus that found in women (e.g., 4.5-7.0kg SMMI) may simply be due to differences in BMI and circulating sex hormones. Further studies need to be done in order to test this hypothesis.

Fatigue has been shown to be related to indices of body composition and anthropometric measurements [11,12,13]. In elderly breast cancer survivors, higher fatigue scores were related to elevated body fat [13]. Even though these authors measured body composition using dual-energy x-ray absorptiometry (DXA), it was

unfortunate that there was no report of the skeletal muscle mass measurement of the leg which could have linked the SMMI with fatigue in this group of patients. Stone et al [11] found that mid-arm circumference was significantly related to subjective measures of fatigue in patients with advanced forms of lung, breast and prostate cancer. An earlier paper published from the same laboratory using a similar subset of advanced cancer patients showed no relationship between fatigue, measures of muscle function (e.g., grip strength and grip fatigue), and measures of body composition (e.g., BMI, triceps skin fold, and limb circumferences)[12]. The use of a single site triceps skin fold and circumferential measure of the mid-arm area is only a gross estimate of local subcutaneous fat and overall arm mass, respectively. Neither limb skin-fold nor circumference provides a direct and accurate assessment of appendicular muscle mass. Thus, these measurement techniques do not specifically assess the different tissue compartments of the limb. This lack of measurement precision and accuracy could partially explain the discrepancies found between our study and others [12,23]. Although not as accurate as magnetic resonance imaging and computed tomography, DXA is a valid assessment technique of body composition that has been shown to be highly reliable in detecting whole body and segmental measurements of skeletal muscle mass [20,34,35]. It has been the modality of choice in aging studies [36,37] and we have shown that the DXA is a precise instrument in the clinical assessment of patients with advanced cancer [22].

When developing multivariate regression models to determine the independent importance of key factors and criteria of CRF, muscle strength as measured by handgrip isometric performance has not generally been shown to be a consistent or

strong predictor of fatigue. When Stone et al [11] controlled for sex, age, diagnosis, concomitant medical illnesses, symptom subscales (e.g., pain), psychological distress (e.g. dyspnea), mid-arm circumference, and grip strength in their multiple linear regression model, only dyspnea, pain and disease burden were related to fatigue. Even though Brown et al [23] found that chair-rise times lengthened with increasing fatigue, they reported no relationship when controlling for fatigue severity, body composition (e.g., skin-fold and limb circumference measurements), subjective weakness measured by a visual analogue scale, or strength (e.g., handgrip) in advanced lung cancer patients. However, based upon a stepwise regression model, Winters-Stone et al [13] found that in a group of long-term breast cancer survivors, lower extremity strength based upon the number of chair sit-to-stand repetitions in 30 s, as well as self-reported physical activity levels, and age were independent predictors of fatigue. The discrepancies among the studies could be partially explained by the variety of different tumour types in the studies as well age and sex. These findings also highlight the multitude of factors and complex interactions that are associated with CRF.

In addition to the independent associations of skeletal muscle mass and strength, our multiple regression models uncovered several other significant and independent correlates of CRF such as weight loss, low albumin levels, depression, prior chemotherapy treatment, and pain. These are all factors that have been frequency linked with fatigue [6, 9]. Thus, the shear number of independent associations reinforces the difficulty in understanding the pathogenesis of CRF. Nevertheless, our study supports the need of an interdisciplinary approach to the assessment and management

of CRF. This approach should include optimal symptom control along with nutritional and exercise interventions [30].

Despite this complex pathophysiology of CRF and the fact that our study was cross-sectional with a single time point measurement, we have established somewhat robust independent relationships among muscle strength, mass, and CRF in this cancer population. However, whether the origin of CRF in this and other studies is related to peripheral or central mechanisms remains to be determined. A classic method to assess peripheral fatigue in cancer patients is to compare the force output of the muscle with electromyographic (EMG) amplitudes and magnetic resonance spectroscopy (MRS). In efforts to measure central influences and what role it plays in CRF mechanisms, novel studies using innovative techniques incorporating transcranial magnetic stimulation (TMS) and magnetic resonance imaging (MRI) will link cerebral motorneuronal activity with regional location. A review of the peripheral and central mechanisms along with a description of the research and clinical tools used to evaluate the possible physiological interactions identifying CRF has been recently published by Davis and Walsh [39].

In summary, our study strongly supports an independent association between muscle strength, mass and CRF. Future studies should confirm a cause-effect nature of this association through a clinical trial by examining the effect of nutritional and exercise interventions on CRF in patients with advanced cancer. Optimal symptom control remains a cornerstone in the treatment of CRF. Modern technology should assist both researchers in better defining the different pathophysiologic mechanisms of CRF and

clinicians in personalizing the treatments of this important and prevalent symptom in advanced cancer patients.

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Conflict of interest statement None

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TABLE 1. Patient demographics and clinical characteristics: summary of the bivariate linear regression; fatigue level (BFI) is the dependent variable.

Variables		Mean ± SD n (%)	B	95% CI
Age (years)		61.6 ± 13.2	0.02	-0.36 to 0.40
Sex	Female	36 (42.8)	0.9	-9.1 to 11.0
	Male	48 (57.2)	1	
BMI (kg/m^2)		24.1 ± 5.4	-1.6†	-2.4 to -0.7
Tumor Type	NSCLC	16.0 (19.0)	-0.8	-13.5 to 11.9
	GI	68 (81.0)	1	
Cancer Stage	Metastatic	48 (57.0)	-4.9	-7.7 to 14.9
	Locally Advanced	36 (43.0)	1	
Chemotherapy	Yes	22 (26.2)	3.6	-7.7 to 14.9
	No	62 (74.8)	1	
Raditherapy	Yes	11 (13.1)	0.1	-14.7 to 14.9
	No	73 (87.9)	1	
Medications impacting on CRF	Yes	29 (34.5)	1.7	-9.0 to 12.5
	No	52 (61.9)	1	
Hemoglobin	<119 g/dL	27 (32.1)	12.0‡	1.6 to 22.4
	≥120 g/dL	56 (66.7)	1	
Albumin	<32 g/dL	11 (13.1)	23.4†	9.4 to 37.3
	≥32 g/dL	73 (85.7)	1	
C-Reactive Protein	>5 g/dL	54 (64.3)	5.6	-7.0 to 14.2
	≤5 g/dL	28 (33.3)	1	
ECOG Performance Status		1.22 ± 0.9	16.1*	12.1 to 20.0

Charlson Comorbidity Index	0.6 ± 1.3	0.08	-3.8 to 3.9
Pain (0-10; 10 worst)	3.3 ± 2.8	2.6*	1.2 to 4.1
Depression (0-10; 10 worst)	3.3 ± 2.7	2.9†	1.2 to 4.6

BMI = body mass index; NSCLC = non-small cell lung cancer; GI = gastrointestinal. ECOG: Eastern Cooperative Oncology Group. * $p < 0.001$, † $p < 0.01$, ‡ $p < 0.05$

TABLE 2. Body composition, muscle strength and muscle quality: summary of the bivariate analysis, fatigue level (BFI) is the dependent variable.

Variables		Mean ± SD	B	95 % CI
Arm Lean Mass (kg)		2.37 ± 0.77	-0.004‡	-0.007 to -0.001
Leg Lean Mass (kg)		7.41± 1.79	-0.001‡	-0.003 to <-0.001
SMMI (kg/m)			-4.8†	-8.4 to -1.3
Sarcopenia[1]	yes		11.4†	1.3 to 21.4
	no		1	
Handgrip Strength (kg)		30.0 ± 10.4	-0.6‡	-1.1 to -0.15
Quadriceps Strength (Nm) (n=57)[2]		76.1 ± 46.7	-0.1‡	-0.2 to -0.01
HGS Muscle Quality [3]		12.7 ± 2.5	-0.6	-2.6 to 1.4
QS Muscle Quality [4] (n=57)		10.0 ± 4.5	-1.2	-2.5 to 0.03

SMMI = skeletal muscle mass index; [1]Sarcopenia was calculated using the male (< 7.26 kg of appendicular [arm + leg] skeletal muscle mass/ht^2) and female (< 5.45 kg of appendicular [arm + leg] skeletal muscle mass/ht^2) cutoffs as determined by Baumgartner el al. (41); [2]57/84 patients were tested for quadriceps strength using the Biodex; Nm = newton meters; [3]Handgrip muscle quality = kg force/kg dominant arm mass; [4]Quadriceps muscle quality= Nm torque/kg dominant leg mass.

* $p < 0.001$, † $p < 0.01$, ‡ $p < 0.05$

TABLE 3. Association of isometric handgrip strength and fatigue levels (BFI) in advanced cancer patients: final multivariate regression model.

Variables	R-square: 0.51	
	B	95% CI
Intercept	57.7†	16.8 to 98.7
HGS (kg)	-0.9†	-1.5 to -0.3
Sex (male 0, female 1)	-17.0†	-29.6 to -4.5
Weight Loss (≤5%=0, >5%=1)	8.7‡	0.6 to 16.8
Albumin (≥3.2 g/dL=0, <3.2 g/dL=1)	21.3†	8.8 to 33.9
Depression (0-10; 10 worst)	2.3†	0.7 to 3.8
Pain (0-10; 10 worst)	2.6†	1.2 to 4.1
Concurrent chemotherapy (no=0, yes 1)	10.5‡	1.5 to 19.5

HGS = handgrip strength; “B” is the unstandardized regression coefficient; 95% CI=confidence interval; * $p < 0.001$, † $p < 0.01$, ‡ $p < 0.05$;

TABLE 4. Association of isokinetic quadriceps extensor strength and fatigue levels (BFI) in advanced cancer patients: final multivariate regression model.

Variables	R-Square: 0.30	
	B	95% CI
Intercept	48.5‡	8.8 to 88.0
QS (Nm)	-0.2‡	-0.3 to -0.01
Pain (0-10; 10 worst)	2.7‡	0.7 to 4.8

QS = quadriceps strength in newton meters; “B” is the unstandardized regression coefficient; 95% CI=confidence interval; * $p < 0.001$, † $p < 0.01$, ‡ $p < 0.05$;

TABLE 5. Association of skeletal muscle mass index and sex on fatigue levels (BFI) in advanced cancer patients: final multivariate regression model

Variables	R-Square: 0.46	
	B	95% CI
Intercept	81.4†	27.1 to 135.2
SMMI (kg/m)	-7.5†	-13.0 to -2.0
Sex (male=0, female =1)	-80.0‡	-142.0 to -18.1
SMMI x Sex	10.8‡	1.2 to 20.5
Albumin (≥3.2 g/dL=0, <3.2 g/dL=1)	21.0†	7.9 to 34.0
Depression (0-10; 10 worst)	1.8‡	0.2 to 3.4
Pain (0-10; 10 worst)	2.3†	0.8-3.9

SMMI= skeletal muscle mass index as calculated by appendicular lean mass / height^2; "B" is the unstandardized regression coefficient; 95% CI=confidence interval; * $p < 0.001$, † $p < 0.01$, ‡ $p < 0.05$

Figure Titles:

FIGURE 1. Correlation between isometric handgrip strength (HGS) and the Brief Fatigue Inventory (BFI) in male (dotted line, n=48) and female (solid line, n=36) patients with newly diagnosed advanced cancer.

FIGURE 2. Correlation between isokinetic (60^{o}/s) quadriceps extension strength (QS) and the Brief Fatigue Inventory (BFI) in male (dotted line, n=33) and female (solid line, n=24) patients with newly diagnosed advanced cancer.

FIGURE 3. Correlation between skeletal muscle mass index (SMMI) and the Brief Fatigue Inventory (BFI) in male (dotted line, n=48) and female (solid line, n=36) patients with newly diagnosed advanced cancer.

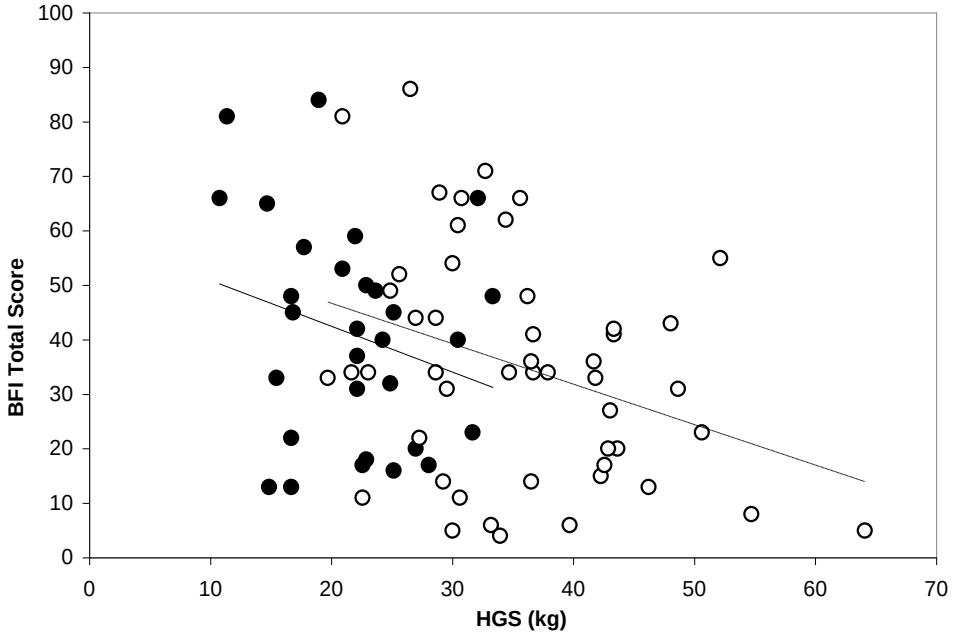
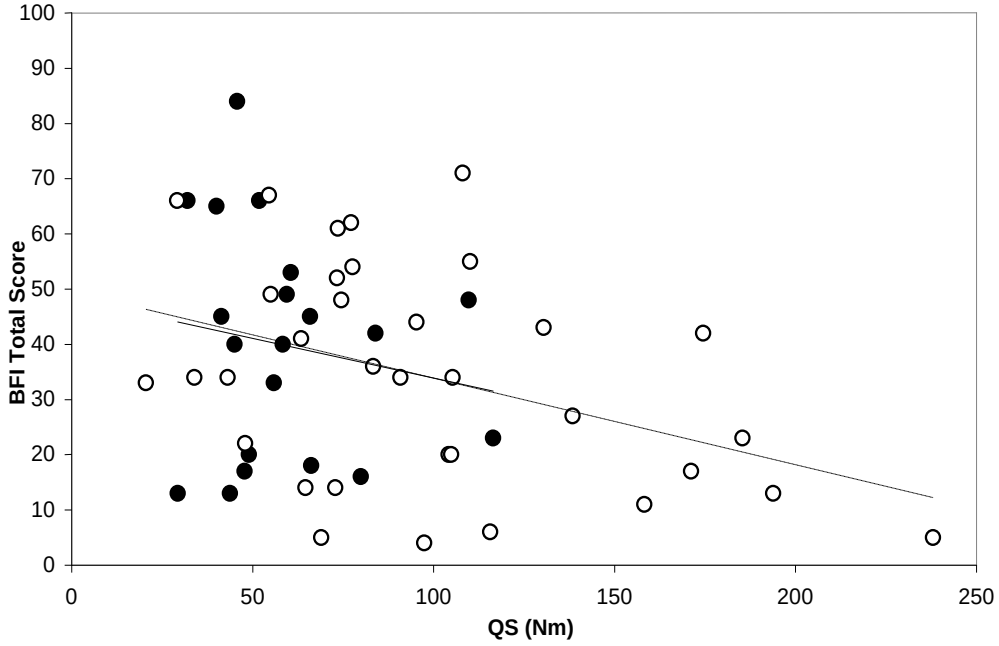


Figure 1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QS (Nm)
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20
30
40
50
60
70
80
90
100
0
50
100
150
200
250

Figure 2

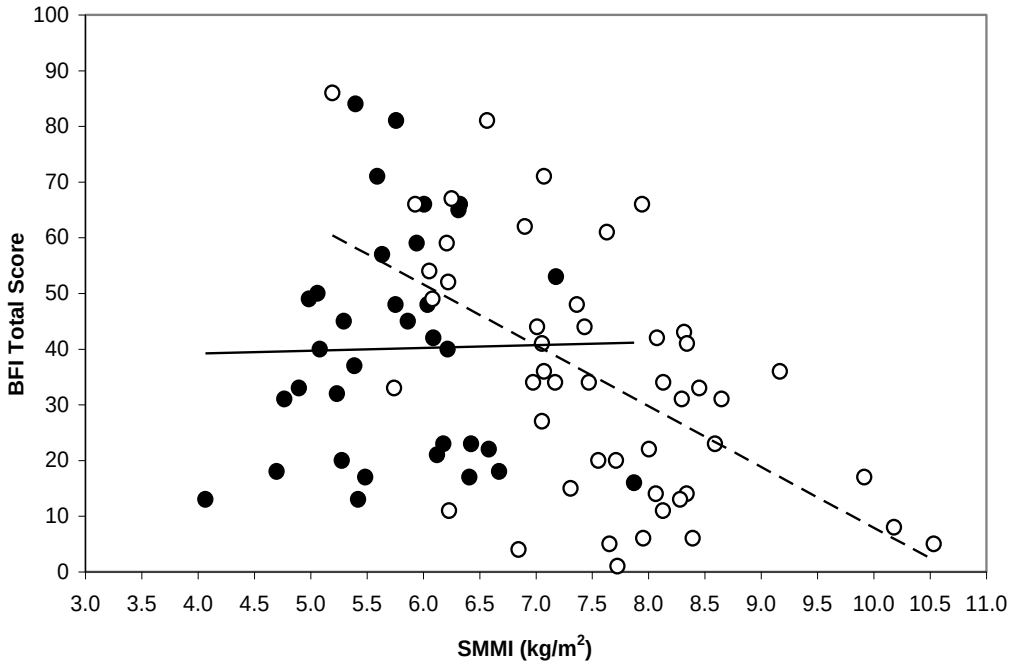
BFI Total Score
100
90
80
70
60
50
40
30
20
10
0
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
9.0
9.5
10.0
10.5
11.0
SMMI (kg/m2)

Figure 3