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Original Article

Determinants of hand grip strength, knee extension strength and functional status in cancer patients

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SUMMARY

Background & aims: Decreased functionality and muscle weakness are prominent features in cancer patients. We investigated determinants of muscle function assessed by hand grip and knee extension strength as well as functional status in cancer patients.

Methods: 189 consecutively admitted cancer patients (age 60.8 ± 12.7 years, 96 male) were recruited. Muscle function was assessed by hand grip and knee extension strength, and percentage of anticipated peak expiratory flow (%PEF). Functional status was determined by the EORTC questionnaire of quality of life. Nutritional status was assessed with Subjective Global Assessment (SGA). Age, gender, SGA, body mass index, clinical variables such as cancer location, presence of distant metastases, tumour burden according to TNM stage, UICC stage, number of drugs per day, number of comorbidities, type of treatment and depression were investigated as potential risk factors for muscle weakness and impaired functional status in a multiple regression analysis.

Results: 80 patients (39 male) were classified moderately or severely malnourished. Malnutrition also emerged as an independent determinant for hand grip (estimated effect size 11%, $p < 0.01$), knee extension strength (estimated effect size 12%, $p < 0.001$), and peak expiratory flow (estimated effect size 30%, $p < 0.008$) and functional status (estimated effect size 19.4%, $p < 0.001$) next to age and gender, which were the strongest predictors. Among the disease parameters, only amount of daily medication exhibited a significant influence on knee extension strength.

Conclusions: Malnutrition is a disease independent risk factor for reduced muscle strength and functional status in cancer patients. Treatment of malnutrition might therefore also restore muscle strength.

1. Introduction

Reduced muscle strength together with an impaired functional status is a well-known phenomenon in patients with chronic or terminal disease and has a negative impact on both wellbeing and outcome. In cancer patients in particular, muscle weakness and physical fatigue are highly prominent features so that in a recently published definition of cancer cachexia, the definition included weight loss of at least 5% in the preceding 12 months plus three out of five clinical symptoms, of which decreased muscle strength was one.[1]

It is therefore not unexpected that hand grip strength, for instance, is an excellent prognostic marker for morbidity and mortality for both acute and long term outcome. Reduced hand grip strength is strongly correlated with postoperative complications[2–4] and has been reported to be both predictive of length of hospital stay[5,6] and loss of functional status in hospitalized patients[6,7] as well as short term survival.[8] Even death within one year of hospitalisation was correlated with hand grip strength in a study of elderly patients admitted for pneumonia. In these patients, hand grip strength was a more powerful predictor than pneumonia severity, age or number of comorbidities.[9] Regarding long term outcome, muscle function assessed by hand grip strength or quadriceps strength but not muscle mass or parameters of body composition is related to all-cause mortality in middle aged and elderly subjects.[9–12] In healthy middle aged men, baseline hand grip strength has even shown to be associated with mortality risk in the subsequent 30 yrs.[13]

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In healthy people, age and gender are the strongest influencing factors on muscle strength.[14] In acute or chronic disease, however, various further factors such as disease severity, co-morbidity load, medical treatment, and immobilisation contribute to muscle weakness and therefore to the patients' decreased wellbeing. Moreover, nutritional status which is frequently reduced in disease invariably has a great impact on muscle strength. In benign disease for instance, disease related malnutrition results in decreased muscle function; we found 25.8% lower absolute hand grip strength values in malnourished hospitalized patients compared to patients who were classified wellnourished. This difference was also seen when stratifying the patients according to their body mass index, implying that loss of weight has more impact on muscle strength than muscle mass itself.[15] Similarly, Vaz et al. showed that hand grip strength did not merely reflect body mass but could also differentiate between chronically energy-deficient and well-nourished but underweight individuals with a similar BMI.[16]

In this prospective cross-sectional observational study we investigated muscle strength assessed by hand grip strength, knee extension strength and percentage of predicted peak expiratory flow as well as functional status in consecutively admitted patients with various types of cancer and aimed at identifying determinants of muscle weakness and impaired functional status in cancer disease.

2. Methods

2.1. Subjects and methods

One hundred and eighty nine patients (96 of whom were male) admitted to the Dept. of Gastroenterology, Hepatology and Endocrinology, to the Dept. of Oncology and Hematology and Dept. of Radiotherapy were included in the study. Patients were recruited if they were older than 18 years and were suffering from solid tumour disease.

Patients with neuromuscular disease, hemiplegia and rheumatoid arthritis were excluded due to the expected reduction in hand grip and knee extension strength.

All measurements were made within 48 h of admission to hospital. All patients gave written informed consent and the Ethics Committee of the Charite Universitätsmedizin Berlin approved of the study. Demographic characteristics, age and gender, as well as clinical variables such as duration of disease (defined as length of time in days since diagnosis), cancer type and location, presence of distant metastases, and tumour burden according to TNM stage, as well as Union Internationale contre le cancre (UICC) stage classification were documented. Moreover, number of drugs per day, number of comorbidities and type of treatment were recorded and Karnofsky Performance scale was determined.

2.2. Anthropometric measurements

Body weight was measured in light clothes with a portable electronic scale (Seca 910, Hamburg, Germany) to the nearest 0.1 kg and height was measured with a portable stadiometer (Seca 220 telescopic measuring rod) to the nearest 0.1 cm. Weight and height were used to calculate body mass index (BMI) (weight [kg]/height [m]^2).

2.3. Subjective global assessment

The Subjective Global Assessment (SGA) was carried out using the protocol developed by Detsky et al.[17] in order to determine nutritional status. It relies on the patient's history regarding weight loss, dietary intake, gastrointestinal symptoms, functional capacity, and physical signs of malnutrition (loss of subcutaneous fat or muscle mass, oedema, ascites). Patients were classified as well-nourished (A), moderately or suspected of being malnourished (B) or severely malnourished (C).

2.4. Muscle function

2.4.1. Hand grip strength

Hand grip strength was measured in the nondominant hand with a Jamar dynamometer (Sammons Preston Rolyan, Chicago, USA). The patients performed the test while sitting comfortably with shoulder adducted and forearm neutrally rotated, elbow flexed to 90°, and forearm and wrist in neutral position. The patients were instructed to perform a maximal isometric contraction. The test was repeated within 30 s and the highest value of three tests was used for the analysis.

2.4.2. Knee extension strength

Knee extension strength was measured while the patients were seated, legs not touching the floor. The right leg was then fixed with a sling which was connected to the wall behind the patients and connected with a force sensor. Patients were then encouraged to perform maximum knee extension. The test was performed three times and the highest value was documented.

2.4.3. Expiratory peak flow

Expiratory peak flow was assessed with the ASSESS Peak Flow Meter (Respironics, HealthScan Inc, NJ, US). Patients were told to exhale as fast and forcefully as possible. The test was carried out three times and the highest reading was recorded. The expiratory peak flow was then expressed as percentage of predicted value.[18]

2.5. Functional status and health related quality of life

Quality of life was determined with the validated core questionnaire QLQ 30 of the European Organisation for Research and Treatment of Cancer (EORTC). The questionnaire assesses quality of life in nine domains. It includes 30 questions exploring five functional scales (physical functioning, role functioning, emotional functioning, cognitive and social functioning), three symptoms scales (fatigue, nausea/vomiting, pain), and six single scales (dyspnoea, insomnia, appetite loss, constipation and diarrhoea, financial impact of disease) as well as one global scale (general health).

For the regression analysis, the scale Physical Function was used as indicator for the functional status since it is derived from the first five questions of the EORTC which regard physical exertion, activity, mobility and self caring capacity.

2.6. Depression

Risk for depression was assessed using the validated German version of the Center for Epidemiological Studies Depression Scale (CES-D).[19]

2.7. Statistical analysis

Statistical analysis was carried out using the software package SPSS 16, SPSS Inc. Chicago, USA. All data are given as mean and standard deviation. Pearson's correlation was calculated to assess the relationship between variables. Multiple comparison between the SGA groups was performed with one-way between groups analysis of variance (ANOVA). Regression analysis was performed with the General Linear Model (GLM) allowing adjustment for continuous and categorical variables, in order to assess the impact of disease related, demographic as well as nutritional parameters on muscle function and functional status. Age, SGA classification,

Table 1
Tumour entities and disease severity.

Localisation	Total	Tumour stages according to UICC			
		I	II	III	IV
GI tract:	103				
Gastro-eosophageal	16	1	2	2	11
Colorectal	37	8	7	7	15
Pancreatic	9	1		1	7
Liver	21	5	5	3	8
Biliary	18	3	3	12	
Peritoneum	2	2			
Head and neck:	30				
Oropharynx	15			2	13
Larynx	6	1		3	2
Nasopharynx	1				1
Tonsil	2				2
Base of the tongue	6				6
Lung	9	4		2	3
Urinary tract:	8	4		2	2
Gynecological:	21				
Breast	10	0	2	1	7
Cervix	9	3	1		5
Ovary	1				1
Uterus	1	1			
Thyreoid gland	5	1		1	3
Others:	13				
Cancer of unknown primary	5	1		1	3
Melanoma	1				1
Bone	1			1	
Adrenal gland	6	1			5

BMI, duration of disease, UICC, number of drugs per day and co-morbidity load were investigated as risk factors. Gender, tumour location as well as type of treatment were introduced as categorical variables. The estimates of effect size are expressed as percentages of eta squared (η^2). An acceptable level of statistical significance was established a priori at $p < 0.05$.

3. Results

One hundred and eighty nine cancer patients were included in the study. Tumour entities and disease stages and further patient characteristics are displayed in Tables 1 and 2. The majority of the recruited patients were suffering from tumour disease of the gastrointestinal tract and the UICC stage 4 was most prevalent. Eighty patients (38 male) were classified moderately or severely malnourished according to the Subjective Global Assessment. Demographic, nutritional and functional characteristics are displayed in Table 2 and Fig. 1. Forty percent of the patients were not receiving active cancer treatment (yet/no longer), 22 percent were receiving chemotherapy, 9 percent radiotherapy, 18 percent combined radio- and chemotherapy and 11 percent other treatment. Fifty three patients (28%) received artificial nutrition; 18 patients (9.5%) oral nutritional supplements, 16 patients (8.4%) enteral nutrition and 19 patients (10.1%) received parenteral nutrition.

The hand grip (HGS) and knee extension strength (KES) were highly inter-correlated (see Fig. 2), whereas peak flow did not correlate as closely with these two parameters. (Hand grip strength and %PEF: overall: $r = 0.352$, $p < 0.001$; men: $r = 0.440$, $p < 0.001$; women: $r = 0.325$, $p < 0.001$. Knee extension strength and %PEF: overall: $r = 0.411$, $p < 0.001$; men: $r = 0.531$, $p < 0.001$; women: $r = 0.277$, $p < 0.001$).

Hand grip strength and knee extension strength were higher in men than women (HGS: 34.6 ± 9.9 vs. 19.6 ± 6.8 kg, $p < 0.0001$; KES 36.7 ± 14.2 vs. 19.9 ± 9.1, $p < 0.001$). They declined slightly with age (HGS: $r = -0.222$, $p = 0.002$; KES: $r = -0.147$, $p < 0.032$) and were moreover correlated with the indicators of functional status, EORTC-Scale Physical Function (PF) as well as Karnofsky Performance Scale (KPS) (HGS: $r = 0.444$, $p < 0.001$ with PF and $r = 0.468$, $p < 0.001$ with KPS; KES: $r = 0.496$, $p < 0.001$ with PF and $r = 0.469$ with KPS; %PEF: $r = 0.311$, $p < 0.001$ with PF and $r = 0.486$, $p < 0.001$ with KPS).

The Karnofsky Performance Scale was negatively correlated with age (KPS: $r = -0.267$, $p < 0.001$).

The impact of demographic characteristics, disease parameters and nutritional parameters on the muscle strength indicators, hand grip and knee extension strength, %peak expiratory flow as well as on functional status was determined in a multiple regression analysis. As can be seen in Table 3, malnutrition classified according to the Subjective Global Assessment emerged as a risk factor for reduced hand grip and knee extension strength as well as reduced %PEF in our study population next to the imperative factors age and gender.

Among the disease variables, only amount of daily medication had an impact on knee extension strength.

The regression models were able to explain 65 percent of the variation of hand grip strength and 55 percent of the variation of knee extension strength. Malnutrition was the only risk factor from this model with impact on the %PEF although the explained variation was altogether low (26%).

3.1. Quality of life

Most functional scales were significantly reduced in malnutrition and the majority of symptom scales were higher in the malnourished patients (see Fig. 3).

Table 2
Demographic, nutritional and functional parameters in all study patients and according to SGA classification and type of treatment.

	ALL $N = 189$	SGA A $N = 109$	SGA B/C $N = 80$	*P*-value
Age	60.8 ± 12.7	59.7 ± 13.0	63.3 ± 12.1	n.s.
Gender (f/m)	93/96	51/58	42/38	n.s.
BMI (kg/m^2)	$25.6 \pm 5.\ 2$	27.0 ± 5.2	23.8 ± 4.7	0.0001
UICC stage I-III/IV	82/107	58/51	24/56	0.006
duration of disease (days since diagnosis)	829.8 ± 1447.0	$927.\ 3 \pm 1369.1$	694.5 ± 1458.0	n.s.
number of drugs per day	5.0 ± 3.4	4.3 ± 3.3	6.0 ± 3.3	0.001
number of comorbidities	3.4 ± 2.3	3.4 ± 2.2	3.6 ± 2.4	n.s.
Hand grip strength (kg)	27.2 ± 11.3	30.4 ± 10.4	22.9 ± 11.1	0.0001
Knee extension strength (kg)	28.7 ± 14.7	32.4 ± 15.3	22.9 ± 11.4	0.0001
Peak expiratory flow (% of predicted value)	80.8 ± 24.7	88.6 ± 23.0	68.5 ± 22.2	0.0001
Karnofsky Performance Scale (%)	70.4 ± 13.0	75.8 ± 10.2	63.1 ± 13.0	0.0001
Depression (pts)	19.1 ± 9.7	17.3 ± 9.0	21.9 ± 10.1	0.003
Physical Function (%)	65.5 ± 27.3	75.2 ± 22.6	51.7 ± 26.8	0.0001

Data displayed as mean and SD. *P*-value is given for the comparison of SGA A and SGA B and C.

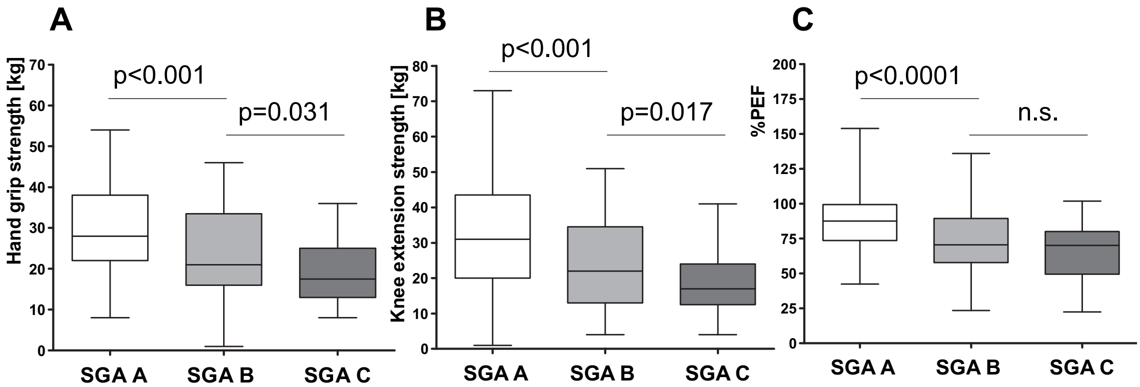

Fig. 1. Muscle function according to the Subjective Global Assessment Groups. SGA A = wellnourished patients, SGA B = moderately malnourished patients, SGA C = severely malnourished patients. The box plots display the minimum, the maximum and the 25th, 50th and 75th percentiles.

As anticipated, risk for depression was the most important risk factor for the EORTC-scale Physical Function, an indicator of functional status (Table 4). Malnutrition and number of drugs per day were identified as further predictors. Due to the high correlations between muscle function and functional status we introduced the muscle function parameters as risk factors for Physical Function in a second step. In the second model, malnutrition lost its independent impact, whereas knee extension strength emerged as significant predictor on functional status ($F = 15.049$; estimates of effect size 16.9%; $p < 0.0001$). Also, age, gender, and BMI were further risk factors and this model explained approximately 60 percent of the variable's variation.

4. Discussion

In this study, disease related malnutrition was identified as one of the contributing factors besides age and gender for impaired muscle strength defined by hand grip strength, knee extension strength as well as percentage of %PEF (percentage of anticipated gender and age stratified peak expiratory flow) in cancer patients. Apart from number of medications per day, a rough surrogate marker for morbidity, tumour disease severity defined by UICC stage, cancer location, and type of treatment did not appear to have an additional impact on muscle strength in this study population. Although chemotherapy has a well-known effect on nutritional status[20] and there is also some evidence from in vitro or animal studies that it exerts a negative impact on muscle per se,[21,22] we found no impact on muscle function in our study population. This is most likely explained by the fact that most variables used in the model were interrelated; type of treatment lost its significance when malnutrition as a much stronger predictor – although to some extent dependent – was entered in the model.

The regression models including demographic, disease and nutritional parameters explained 55 and 65 percent of the variation of knee extension and hand grip strength, respectively. The explained variation of hand grip strength is slightly lower but comparable to the explained variation of hand grip strength in healthy subjects by a model comprising age, gender, appendicular muscle mass and physical activity.[14]

In our model, malnutrition was the only significant risk factor for reduced %PEF which is in contrast to earlier studies showing that although lower respiratory muscle performance is associated with malnutrition, %PEF is not necessarily reduced.[23] The explained variation found in our study, however, was altogether rather low. Clearly, further factors such as smoking habits or chronic obstructive pulmonary disease etc., which were not included in our regression model, are responsible for the reduced strength of the respiratory muscles.

Muscle function as assessed by hand grip and knee extension strength correlates with measures of functional status and with the physical components of quality of life, so they can be expected to have similar determinants.

Malnutrition was also a risk factor for impaired functional status as determined by the EORTC-scale Physical Function, which corroborates the findings by Ravasco et al. who demonstrated an impact of weight loss, energy and protein intake on the global function scales of the EORTC. However, when introducing muscle function parameters (HGS; KES and PEF) as additional risk factors in the regression analysis, malnutrition was no longer an independent determinant of functional status ($p = 0.09$) whereas knee extension strength emerged as a predictor for reduced functionality. Hand grip strength however did not predict functional status in our study population. This might be explained by the fact that the EORTC questionnaire largely regards activities which claim muscle function of the lower extremities (e.g. walking distances). As also stated by Kuh et al. hand grip strength and muscle function parameters of lower extremities have different requirements and should not be

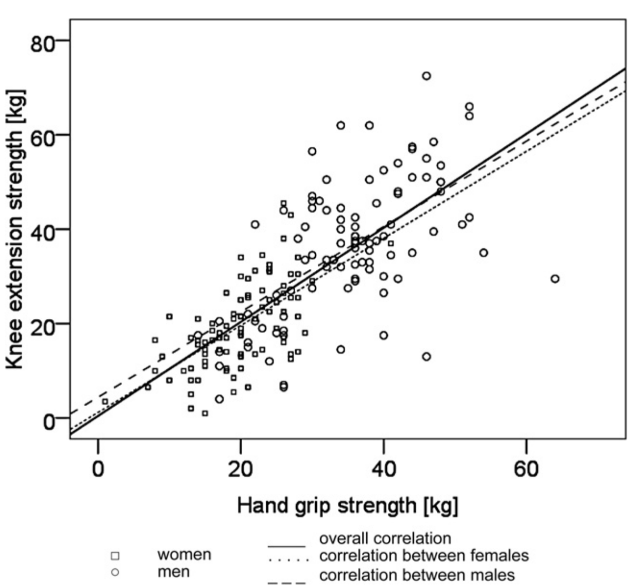

Fig. 2. Correlations between the muscle function parameters. Hand grip and knee extension strength: overall: $r = 0.752$, $p < 0.001$; men: $r = 0.594$, $p < 0.001$; women: $r = 0.629$, $p < 0.001$.

Table 3
Results from the univariate multiple regression analysis: impact on muscle function parameters. Explained variation of hand grip strength by the model = 0.650, for knee extension strength 0.552, for %PEF = 0.256, <0.0001.

	Hand grip strength			Knee extension strength			% Expiratory peak flow[a]		
	F— test	Estimates of effect size (%)	*P*-value	*F*-test	Estimates of effect size (%)	*P*-value	*F*-test	Estimates of effect size (%)	*P*-value
Age	16.343	14	<0.0001	10.150	11	<0.0001	0.985	30	n.s.
Gender	108.677	59	<0.0001	66.037	52	<0.0001	0.566	3	n.s.
SGA	12.369	11	<0.001	10.562	12	<0.001	7.167	30	0.008
BMI	4.052	4	0.046	2.949	3	n.s.	0.672	3	n.s.
Depression	1.664	2	n.s.	2.171	2	n.s.	0.947	4	n.s.
UICC	0.143	0.1	n.s.	0.762	1	n.s.	2.188	10	n.s.
Tumour location	0.763	4	n.s.	0.477	3	n.s.	1.394	35	n.s.
Type of treatment	0.518	3	n.s.	1.015	8	n.s.	0.242	7	n.s.
Number of comorbidities	1.039	1	n.s.	0.160	0	n.s.	0.172	1	n.s.
Number of drugs/day	2.608	2	n.s.	5.477	6	0.021	0.491	2	n.s.

[a] patients with tracheostomy were excluded from measurement of exspiratory flow ($n = 7$).

used as surrogates for each other when assessing physical performance.[24]

It is however tempting to conclude that the impact of an impaired nutritional status on perceived decreased functionality is mainly inflicted by reduced muscle strength.

Several authors have reported decreased muscle function in malnourished patients such as elderly or surgical patients,[25–29] malnourished peritoneal dialysis patients,[30] or anorexia nervosa patients.[31] It is known that patients who have lost more than 20% of their body weight inevitably suffer from physiological impairment[32] since muscle function, as assessed by hand grip strength, is related to loss of total body protein.[32]

As alterations of body composition, including loss of muscle mass, can occur before weight loss is observed, a decrease in muscle function frequently precedes determinable weight loss in disease. Moreover, muscle function is likely related to further factors than pure muscle mass, such as electrolytes, energy rich phosphates and membrane potential, which explains why muscle function responds earlier to nutritional deprivation and restoration than body compartments.[31,33–35] This sensitivity might account for the clinical prognostic relevance of hand grip strength.

In disease related malnutrition, all of these parameters are however most likely affected which makes our finding that disease related malnutrition is a major determinant of hand grip strength hardly unexpected. In our study population, malnutrition occurred most frequently in UICC stage IV, which is an anticipated finding and emphasizes the close relationship between disease and malnutrition. It remains a difficulty to distinguish between disease-induced symptoms or effects due to an impaired nutritional status. However, in our study population, disease parameters did not appear to have any further significant impact on the muscle function parameters or functional status in the presence of malnutrition and this suggests that muscle weakness is largely due to the impaired nutritional status which is potentially reversible and does not result entirely from tumour disease or its treatment.

In a retrospective analysis by Fearon et al. weight loss ≥ 10 percent by itself did not explain the impact on physical function and outcome in a study population of weight losing patients with pancreatic cancer.[36] Only a three factor profile with weight loss, inflammation and reduced nutritional intake corresponded with reduced physical function. This apparent difference to our study might be due to our study population who differed in cancer entities and nutritional status, as we consecutively recruited all patients and did not focus on cachectic patients only. Moreover, the SGA is a more complex feature than weight loss alone including questions about nutritional intake and gastrointestinal symptoms and taking into account physical symptoms such as loss of subcutaneous fat or muscle. Also, if a patient regains non-oedematous weight this is considered as a sign of anabolism and the patient is classified wellnourished even if his net weight loss is substantial.

Furthermore, in our study, CRP was available only in a subgroup ($n = 93$), but was not a significant predictor when introduced in the regression model for hand grip strength ($p = 0.058$) and showed no significant impact on knee extension strength or parameters of

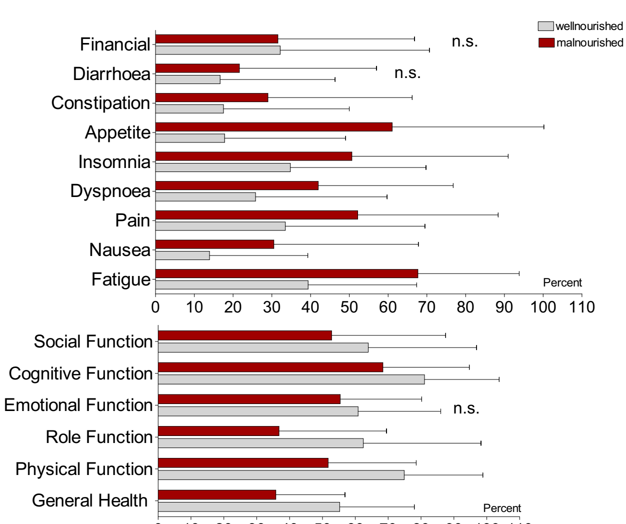

Fig. 3. EORTC Quality of life scores according to wellnourished (SGA A) and malnourished patients (SGA B&C). All scales except Financial Problems, Emotional Function and Diarrhoea were significantly different between the groups.

Table 4
Results from the univariate multiple regression analysis: impact on functional status. Explained variation of the EORTC-scale Physical Function: $r^2 = 0.518$.

	EORTC-scale Physical Function		
	F-test	Estimates of effect size (%)	*P*-value
Age [yrs]	0.004	0	n.s.
Gender	0.396	0.6	n.s.
SGA	15.276	19.4	<0.0001
BMI	1.582	2.2	n.s.
Depression	39.952	43.7	<0.0001
UICC	1.569	2.2	n.s.
Localisation	0.920	42	n.s.
Type of treatment	1.104	10.3	n.s.
Number of comorbidities	0.006	0	n.s.
Number of drugs/day	10.881	14.2	<0.001

functional status, also when only considering patients with elevated CRP ($n = 54$) (data not shown). However, this may be due to the small remaining sample size so that inflammation cannot be disregarded as a potential impact factor on reduced muscle function.

In conclusion, disease related malnutrition is an independent determinant of the muscle function parameters hand grip strength, knee extension strength and %PEF in cancer patients.

In benign disease, nutritional therapy improves muscle function,[37] but treatment of malnutrition requires further study in cancer patients.

Conflict of interest

The authors declare that they have no conflict of interest.

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KN, CS and MP: concept of the study, KN and MP: writing of the manuscript, RS and KN: statistical analysis; NS and DZ recruitment and assessment of patients, HL, LV and CS critical input and revision of the manuscript.

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