Review

Clinically relevant determinants of body composition, function and nutritional status as mortality predictors in lung cancer patients

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ABSTRACT

Lung cancer belongs to the type of tumors with a relatively high frequency of malnutrition, sarcopenia and cachexia, severe metabolic syndromes related to impairment of physical function and quality of life, resistance to therapy and short survival. Inexpensive and accessible methods of evaluating changes in body composition, physical function and nutrition status are for this reason of great importance for clinical practice to enable the early identification, monitoring, preventing and treatment of these nutritional deficiencies. This could lead to improved outcomes in the quality of life, physical performance and survival of patients with lung cancer. The aim of this article is to summarize the recent knowledge for the use of such methods, their predictability for patient outcomes and an association with other clinically relevant parameters, specifically with lung cancer patients, because such an article collectively describing their practical application in clinical practice is lacking. The interest of this article is in the use of anthropometry, handgrip dynamometry, bioelectrical impedance analysis derived phase angle and nutritional screening questionnaires in lung cancer patients.

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1. Introduction

Many serious illnesses (e.g. cancer, sepsis or AIDS) are associated with a severe metabolic syndrome called cachexia. The important clinical symptoms include involuntary weight loss accompanied by sarcopenia (skeletal muscle wasting and weakness), fatigue, anorexia, metabolic imbalance and signs of systemic inflammation. Cachexia cannot be fully reversed by conventional nutrition support [1].

In recent years, the staging of cachexia has occurred. An international panel of experts have created a three-stage classification specific for cancer cachexia: precachexia, cachexia and refractory cachexia. Precachexia is a state characterized by early clinical signs and metabolic disturbances preceding substantial weight loss. The criteria for cachexia are considerable body weight loss (more than 5% over the past 6 months) or a body mass index (BMI) of less than 20 in combination with weight loss (more than 2% over the past 6 months) or sarcopenia (appendicular skeletal muscle index determined by dual energy X-ray absorptiometry of lower than 7.26 and 5.45 kg m^{-2} in men and women, respectively) in combination with body weight loss (more than 2% over the past 6 months), but have not entered the refractory stage. Refractory cachexia is a stage characterized by low performance status and low life expectancy (less than 3 months) due to very advanced or rapidly progressive cancer that is unresponsive to therapy [2,3].

Lung cancer belongs to the type of tumors with a relatively high frequency of malnutrition, sarcopenia and cachexia, as demonstrated by the result of recent works. According to the Mini Nutrition Assessment (MNA), 26% of patients with advanced non-small cell lung carcinoma (NSCLC) were malnourished and another 46% of patients were at risk of malnutrition [4]; according to Subjective Global Assessment (SGA), 60% of patients were malnourished [5]. Prado et al. demonstrated that the majority of overweight NSCLC patients (more than 53%) were sarcopenic [6]. According to cancer-specific cachexia classifications (as mentioned above), 18% of NSCLC patients were diagnosed as cachectic, 23% of patients were diagnosed as in a state of precachexia [7].

Cachexia and muscle wasting are related to the impairment of physical function [8], quality of life [5], resistance to therapy [9]

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and shorter survival rate [10]. Early identification, monitoring, prevention and treatment of these nutritional deficiencies could lead to improved outcomes in the quality of life, physical performance and survival of patients with NSCLC. There are several inexpensive and accessible methods of evaluating changes in body composition, physical function and nutritional status including anthropometry, handgrip dynamometry, bioelectrical impedance analysis derived phase angle and nutritional screening questionnaires. The aim of this article is to summarize the recent knowledge of the use of these methods, their predictability of patient outcomes and the association of other clinically relevant parameters, specifically with lung cancer patients. Such an article collectively describing their practical application in clinical practice is lacking.

2. Anthropometry

2.1. Basic anthropometric parameters

For a relatively long time weight loss has been known as an important prognostic factor in lung cancer patients [11,12]. Perhaps the first work of trying to determine the prognostic value of basic anthropometric parameters like triceps skinfold thickness (TST), arm and wrist circumference and their association with clinical and biochemical parameters in NSCLC patients were the study of Ferrigno and Buccheri [13]. The statistical analysis proved an association of all three determined anthropometric parameters with body weight. In addition TST correlated with albumin; arm circumference correlated with albumin, haptoglobin and Eastern Cooperative Oncology Group Performance Status (ECOG) score; wrist circumference correlated with creatinine and ECOG score. Although the univariate survival analysis showed the significant impact of TST and arm circumference on prognosis, the results of multivariate analysis did not confirm these parameters as independent prediction factors. Later it was described in NSCLC patients with weight loss the negative correlation of TST and adiponectin ($r = -0.576$; $P = 0.010$) and the positive correlation of TST and free ($r = 0.888$; $P < 0.001$) and total leptin ($r = 0.892$; $P < 0.001$) [14]. The use of combined anthropometric scores could be superior to isolated anthropometric parameters as demonstrated by Tartari et al. [15]. They combined mid-arm circumference and TST and assessed the mid-arm muscle circumference (MAMC) as follows:

$$MAMC\,(cm) = mid - arm\,circumference\,(cm) - (3.1415 \cdot TST\,(mm))$$

After categorizing the patients according to the percentage of gender and age adjusted expected reference values they found that depleted patients (MAMC below 90% of expected values) had more than twice as short overall survival than patients with normal values of MAMC (90% of expected values and higher) (137 versus 306 days; $P = 0.001$). Also the results of the multivariate survival analysis confirmed the MAMC as an independent prognostic factor. Physiological ranges of the MAMC for men over 20 years are 27.5–41.2 cm and for women 24.5–42.1 cm [16].

2.2. Body mass index

In the past years there have appeared several works concerned with the effect of BMI value on survival in lung cancer patients. Leung et al. [17] described a relatively specific association of obesity (BMI higher than 30) and the reduction of lung cancer deaths (adjusted hazard ratio 0.55; $P < 0.001$), while obesity has no significant effect on other smoking-related and non-tobacco related malignancies. BMI was shown as an independent predictor of survival in this study. Longer median survival rates in obese lung cancer patients in comparison with non-obese patients were confirmed by Yang et al. [18] (13 months in obese versus 8.4 months in

non-obese patients), this effect was independently significant on cancer stage or histological type. The opposite effect on survival time was found in cases of weight loss (6.4 and 9.2 months for patients with and without weight loss, respectively). These results were evaluated by multivariate survival analysis: absence of obesity was found to be an independent predictor of a worse survival rate (hazard ratio 1.12; $P < 0.001$) and absence of weight loss to be an independent predictor of a longer survival rate (hazard ratio 0.087; $P < 0.001$). The results of the association of BMI value with the survival of lung cancer patients (patients with the lowest BMI have the shortest survival) was also demonstrated by other studies [19–21].

2.3. Advanced lung cancer inflammation index (ALI)

An interesting approach enabling the enhanced prediction of survival of advanced lung cancer patients was brought about by Jafri et al. [22]. They combined the BMI value with markers of systemic inflammation, serum albumin level and neutrophil to lymphocyte ratio (calculated as the ratio of absolute neutrophil and lymphocyte count), and created the so called advanced lung cancer inflammation index (ALI):

$$ALI = \frac{BMI\,(kg\,m^{-2}) \cdot serum\,albu\min(g\,dl^{-1})}{neutrophil\,to\,lymphocyte\,ratio}$$

When choosing the cutoff value of ALI 18, the patients with low ALI values were found with a worse performance status, progression free (2.4 versus 5.1 months; $P < 0.001$) and overall survival rate (3.4 versus 8.3 months; $P < 0.001$). The multivariate analysis confirmed the ALI value as an independent predictor of the outcome (hazard ratio for progression free survival was 1.66, $P = 0.003$ and for overall survival 1.42, $P = 0.047$).

2.4. Lumbar skeletal muscle index (LSMI)

As cancer patients show large variability in body composition, muscle wasting is present, even in obese persons, estimation of skeletal muscle mass is of high importance. The higher predictive value of muscle mass determined by weight loss was shown in obese patients with lung and gastrointestinal cancer [10]. The presence of sarcopenia in these patients has proven to be an independent predictor of mortality according to both univariate and multivariate survival analysis (hazard ratio 4.2, $P < 0.001$), while weight loss was not significantly associated with mortality. Patients were classified as sarcopenic according to the value of lumbar skeletal muscle index (LSMI) (men below 52.4 cm m^{-2}, women below 38.5 cm m^{-2}) determined from the computed tomography scan as follows:

$$LSMI\,(cm\,m^{-2}) = \frac{m\,uscle\,cross - sec\,tional\,area\,L3\,(cm^2)}{height\,(m^2)}$$

Martin et al. [21] described the prognostic value of LSMI as further enhanced when combined with other computed tomography scan derived parameter, muscle attenuation, and weight loss. They computed the BMI-dependent threshold values associated with a low survival for these parameters (see Table 1). Stratifying patients according to these threshold values were discovered to have a close association between the number of presented prognostic variables (sarcopenia, low muscle attenuation and body weight loss) and patient survival: median survival rate of patients with zero variables was more than 24 months, patients with one or two variables 16 months and patients with 3 variables with only about 8.5 months. The survival rate of patients with a low BMI was short regardless of the number of presented prognostic variables.

Table 1
Threshold values associated with low survival.

BMI (kg m^{-2})	Skeletal muscle index (cm m^{-2})		Skeletal muscle attenuation (Hounsfield unit)		Body weight loss (%)	
	Men	Women	Men	Women	Men	Women
<25	43	41	41		8	
≥25	53		33			

BMI—body mass index.
Adapted from Martin et al. [21].

3. Handgrip dynamometry

From a variety of methods to assess muscle strength, handgrip dynamometry has been shown to be a reliable and valid method, with benefits as being simple, fast performance and inexpensive. There is also growing evidence that handgrip strength is associated with nutritional and functional status, body composition, inflammation and predicts the survival rate of both healthy persons and persons with several clinical conditions like elderly persons, chronic inflammation and cancer [8,23,24].

3.1. Handgrip strength

The lower handgrip strength of advanced lung cancer patients in comparison to healthy persons was described by Brown et al. [8]. Several studies have shown the association of handgrip strength and other clinically important indexes. The association of decreased muscle strength and malnutrition in lung cancer patients was demonstrated by Piskorz et al. [25]. When they divided patients into 2 groups depending on their weight loss (the cutoff value was chosen to be 6% weight loss), they found a significant decrease in strength and movement speed (tested by tapping test), both in the right and left hand, in the subgroup of weight lose patients. Interestingly, there has been shown a positive correlation between handgrip strength and albumin concentration ($r = 0.4072$ and 0.3406, for left and right hand respectively, $P < 0.01$) and the negative correlation between hand movement speed and albumin concentration ($r = -0.4410$ and -0.4036 for left and right hand respectively, $P < 0.001$). There has also been described a significant association of handgrip strength with phase angle [26] and with sarcopenia (determined according to the appendicular skeletal muscle index value) [6].

3.2. Handgrip strength reference values

A valuable innovation was using handgrip strength reference values [27–29] (see example in Table 2). The first work using this approach in advanced (lung and gastrointestinal) cancer patients was published by Kilgour et al. [30]. They found that more than 70% of these patients have a handgrip strength below 50th percentile and more than 25% of patients below 10th percentile. When comparing the patients with a handgrip strength below 10th percentile and above 50th percentile, the multivariate analysis revealed a significant association of handgrip strength with many important laboratory (lower concentrations of albumin and hemoglobin), body composition (lower amount of lean and fat mass), functional and quality of life characteristics (worse score in many cancer patients questionnaires—Edmonton Symptom Assessment System, ECOG, Brief Fatigue Inventory and McGill Quality of Life Questionnaire). The group with the lowest handgrip strength showed an almost ten times higher incidence of sarcopenia (determined according to appendicular skeletal muscle index value) and more than three times higher probability of dying (hazard ratio 3.2; 95% CI 2.0–5.1; $P < 0.001$) in comparison with the reference group (patients with handgrip strength above 50th percentile).

4. Bioelectrical impedance analysis derived phase angle

Bioelectrical impedance analysis (BIA) is a method that has been used for more than 20 years to estimate body composition, both in healthy persons and in a variety of patient populations including cancer patients [31,32]. BIA is based upon a conductance of an alternate electrical current through body fluids. Whole-body impedance is a combination of resistance (opposition offered by the body to the flow of an alternate electrical current, primarily related to the amount of water present in the tissues) and reactance or capacitance (resistive effect produced by the tissue interfaces and cell membranes). Capacitance causes the current to lag behind the voltage creating a phase shift, which is quantified as the phase angle. Phase angle can be directly calculated as arc tangent of capacitance to resistance ratio [33]. Phase angle has been suggested to be an indicator of cellular membrane damage where higher values reflect better cell membrane integrity and cell function and as a prognostic marker in several clinical conditions such as liver cirrhosis, amyotrophic lateral sclerosis, hemodialysis and peritoneal dialysis, HIV infection and cancer [32,34–37]. Mostly used, both in practice and clinical studies, is the phase angle determined at a frequency of 50 kHz.

4.1. Phase angle

Differences in tissue electric properties between advanced lung cancer patients (stage IIIB and IV) and healthy persons were demonstrated by Toso et al. [38]. Their results showed a significant decline of impedance vector (phase angle) measured at 50 kHz in lung cancer patients in comparison to healthy subjects (matched for sex, age and BMI). This decline was caused by decreased values of capacitance, while resistance values had not changed significantly. There was also described the association of phase angle and patient survival when the median phase angle value was chosen as a cutoff point (median survival of 4 months in patients with a phase angle of 4.5° and lower, versus 12 months in patients with a phase angle higher than 4.5°). Both univariate and multivariate survival analysis have evaluated the phase angle as an independent predictor of survival. The association of phase angle and survival in advanced NSCLC patients was confirmed by Gupta et al. [39]. The phase angle (together with stage at diagnosis and treatment history) was proven to be the independent predictor of mortality according to the multivariate survival analysis. This analysis found that by every degree increase in phase angle there was an association with a relative risk of 0.79 (95% CI: 0.64–0.97, $P = 0.02$), after adjusting for age, stage at diagnosis and prior treatment history. Survival of patients with phase angle values higher than median (5.3°) was significantly longer than of patients with median and lower phase angle values (median survival 12.4 versus 7.6 months). This study also revealed the gender specific differences of phase angle values, males had significantly higher values than females (5.6° versus 4.9°).

It was demonstrated that the phase angle correlates not only with mortality, but also with some markers of performance status or illness severity in lung cancer patients. Castanho et al. [40] showed the negative correlation of phase angle and tumor mass volume estimated by means of helical tomography ($r = -0.55$;

Table 2
Reference values of handgrip strength.

Age (years)	Handgrip strength (kg)—dominant hand		Handgrip strength (kg)—non-dominant hand	
	Men	Woman	Men	Woman
18–30	30–57	16–30	30–54	13–29
31–59	27–55	16–35	26–61	10–29
≥60	18–44	11–29	18–45	10–27

Adapted from Budziareck et al. [29].

$P < 0.001$), positive correlation of phase angle and Karnofsky performance status (KPS) score ($r = 0.44$; $P < 0.05$). The relationship among phase angle, tumor volume and KPS score confirmed also the multivariate variation analysis. In this work there has also been demonstrated that patients with the lowest values of phase angle had the lowest survival. Navigante et al. [26] demonstrated in NSCLC patients with fatigue the significant association of phase angle and hand grip work estimated by means of dynamometry according to the formula:

$$Grip\ work = (max\ imal\ strength \cdot 0.75) \cdot fatigue\ resis\tan ce,$$

where fatigue resistance was scored as time in seconds for the pressing of the sphygmomanometer with at least 50% of maximal strength (the measurement was performed with the non-dominant arm). When the patients were divided into subgroups according to phase angle value, the subgroup with lower phase angle value ($<4°$) had also lower values of muscle strength parameters in comparison to patients with normal phase angle ($>4°$) e.g. grip work 113 versus 1365 kg s, $P = 0.004$; median grip strength 17.6 versus 27.0 kg, $P = 0.018$ and maximal grip strength 20.3 versus 30.1 kg, $P = 0.014$).

4.2. Phase angle reference values

The results of the previously mentioned studies could be applicable in the general clinical setting with difficulties, as they mostly use cutoffs within their study population. The first study concerning reference values of phase angle was published in 2005 for a US population, with values stratified according to sex and age [41]. In 2006 Bosy-Westphal et al. [42] published the reference values of phase angle for a German population classified according to all major determinants—sex, age and BMI. The study population consisted of more than 15,000 children and adolescents and almost 215,000 adults. The suitability and clinical relevance of the fifth percentile of sex-, age- and BMI-stratified phase angle reference values (see example in Table 3) in cancer patients was demonstrated by Norman et al. [43]. Patients with a phase angle value below the fifth reference percentile had significantly deteriorated nutritional (increased percentage of malnourished patients) and functional status (lower handgrip strength, KPS score and peak expiratory flow), decreased quality of life (lower values of physical, role, cognitive and social function and higher incidence of symptoms like fatigue, nausea, vomiting, constipation, appetite loss, dyspnea and pain) and an increased risk of depression and six month mortality (hazard ratio 4.0; 95% CI 2.4-6.8; $P < 0.001$).

4.3. Standardized phase angle

Phase angle reference values also allow standardization e.g. creation of Z score for determining the individual deviations from the reference values. Standardized phase angle can be determined as follows:

$$s\tan dardized\ phase\ angle = \frac{observed\ phase\ angle - mean\ phase\ angle}{s\tan dard\ deviation\ of\ phase\ angle},$$

where mean and standard deviation are from reference values. The standardized phase angle was found to be an independent predictor for impaired nutritional and functional status and survival. Its predicting power for six month mortality was even better than when assessed by the SGA score or disease severity [43]. The usefulness of standardized phase angle in predicting mortality in cancer patients receiving chemotherapy was evaluated by Paiva et al. [32]. They choose as the cutoff value of the standardized phase angle to be −1.65, which stands for the fifth percentile and therefore could be considered as the lower limit. Survival time between patients with a low value of standardized phase angle was significantly shorter (12 months versus at least 36 months, $P < 0.001$). Both univariate and multivariate survival analysis confirmed standardized phase angle to be an independent risk factor for mortality. Patients with low values of standardized phase angle showed a 2.35 times higher risk of mortality ($P = 0.001$) in comparison with the group of patients with a value of standardized phase angle to be −1.65 and higher. Evaluation of these results specifically for lung cancer patients has not yet been performed.

5. Nutritional screening questionnaires

To screen and assess malnutrition, several nutritional screening questionnaires combining objective and subjective parameters were developed e.g. the SGA, the Patient generated SGA (PG-SGA), MNA or Nutritional risk screening 2002 [44–46].

5.1. Patient generated Subjective Global Assessment

Nutritional risk assessment according to the SGA were developed in the 1980s and in 2006 modified for use in oncological patients; this modification was called PG-SGA. It includes items determining weight loss, food intake alterations, symptoms of nutrition alterations, limitations of functional capacity, presence of metabolic stress and a physical examination (loss of skeletal muscle and subcutaneous fat, presence of edema). According to the resulting score, patients are categorized into three categories: A—well nourished; B—moderately malnourished or suspected malnutrition; C—severely malnourished [44].

Li et al. [47] determined malnutrition in patients with lung cancer according to the PG-SGA. The results demonstrated that 40% of patients were severely malnourished and more than 40% of patients were moderately malnourished or in suspected malnutrition. The mean PG-SGA score was significantly higher in patients with lung carcinoma compared to patients in benign condition. When establishing the regression equation for predicting disease status, the PG-SGA score was found in the equation, while the SGA score was not. This could indicate that PG-SGA is better than SGA in distinguishing those who are lung cancer patients. Sanchez-Lara et al. [5] evaluated the association of malnutrition determined according to the SGA and health-related quality of life and survival in NSCLC patients. Results of this study demonstrated a significant association between SGA-determined nutritional status and a whole range of quality of life parameters e.g. physical and role functioning, fatigue or loss of appetite. Bivariate survival analysis demonstrated the association of the SGA with overall survival (median survival of

Table 3
Fifth percentile values of phase angle–sex, age and BMI stratification.

BMI (kg m^{-2})	Phase angle (°)–fifth percentile			
	Woman 60–69 years	Woman □69 years	Men 60–69 years	Men □69 years
18.5–25	4.41	3.85	4.23	3.82
>25–30	4.58	4.17	4.92	4.20
>30–35	4.55	4.22	4.85	4.27
>35–40	4.47	4.12	4.70	4.22
>40–50	4.42	3.98	4.45	3.63

Adapted from Bosy-Westphal et al. [42].

17 months in the group of well-nourished patients versus 9 months in the group of malnourished patients, $P = 0.001$). The multivariate analysis confirmed the SGA to be an independent predictor of overall survival (hazard ratio 2.7; 95% CI 1.3–5.5; $P = 0.005$).

5.2. Mini nutrition assessment

In 1996 a nutrition screening and assessment tool called the MNA was developed and validated. This original version is composed of 18 items involving general, anthropometric, dietary and subjective assessment data. The maximum achievable score is 30 and subjects are divided into 3 categories according to score reached: well-nourished (scores 23.5 and higher), in risk of malnutrition (score between 17 and 23.5) and malnourished (scores less than 17) [45,48]. The short form of the MNA (created in 2001) consists of 6 items which enables time savings while accuracy is preserved. The maximum score for the short version is 14. Persons who reach a score of 12–14 points are considered well-nourished, persons with a score of 8–11 are at risk of malnutrition and persons with a score of less than 8 are malnourished. A high correlation between the short version and the original one has been confirmed, so MNA could be used in a 2-step process—the short version for screening and the full version for assessment [49].

The MNA was formerly used only for malnutrition screening in elderly people however nowadays it is used also in patients suffering from dementia, pressure ulcers, hematologic malignancies and solid tumors [50–53]. Usefulness of this method for malnutrition screening was also demonstrated in a group of patients with metastatic lung cancer [4]. According to the results of the MNA score, more than two thirds of patients were at risk of malnutrition or already malnourished. The proportion of patients requiring nutritional intervention determined according to their weight loss history was lower (45% of patients had a weight loss of higher than 5% during the preceding 3 months). It has been proven that the MNA was a better determinate than weight loss history, with most of the clinical and laboratory data indicating an adverse outcome (worse performance status, higher number of metastatic sites, presence of brain metastasis, increased calcium and LDH levels), malnutrition (anemia, hypoalbuminemia and low creatinine clearance) and inflammation—cachexia (decreased transferrin levels, increased CRP, IL-6 and IL-8 levels). Both MNA and weight loss history were significantly correlated with the response to first-line therapy, while only MNA with a clinical decision taken by the treating physician for less toxic therapy and with the requirement and duration of hospitalization. Both univariate and multivariate survival analysis have proven a significant association of MNA with the time to progression and overall survival (other independent predictors of overall survival were albumin level and performance status). The number of metastatic sites was the only other predictor of time to progression. On the contrary, only univariate analysis proved a correlation with weight loss history and these parameters. Further studies evaluating the association of MNA and laboratory parameters related to cachexia development confirmed the results of the previous study. The MNA was significantly associated with levels of hemoglobin, albumin, CRP, adiponectin, leptin and IL-8. Univariate and multivariate survival analysis confirmed the MNA as an independent predictor of overall survival and time to progression [54,55]. Another study tried to evaluate the possible link among nutritional status, acute phase response and depression or anxiety in lung cancer patients. It was found that the MNA score is significantly associated with acute phase response (determined as Glasgow prognostic score) and depression, while it is not associated with anxiety (determined as Hospital anxiety and depression scale [56]). The acute phase response correlated significantly both with depression and anxiety. The significant association of the MNA and the Glasgow prognostic score with overall survival was proven by multivariate survival analysis. Depression and anxiety had no significant influence on overall survival [57].

6. Summary

This article illustrates the clinical relevance of methods like anthropometry, handgrip dynamometry, bioelectrical impedance analysis derived phase angle and nutritional screening questionnaires to predict the outcome of lung cancer patients based on the results of many recent works. These methods should undergo further research which could improve their further use in clinical practice.

Conflict of interest statement

The authors declare that they have no conflict of interest.

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