



# Sarcopenia in non-small cell lung cancer patients underwent pulmonary surgery: clinical outcome and cost effectiveness

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**Background:** Lung cancer is the leading cause of cancer death in several countries. Surgical resection is a potentially curative treatment for non-small cell lung cancer (NSCLC), but tumor-specific factors and patient physical factors are important for postoperative prognosis. We conducted a retrospective study to investigate the link between sarcopenia and postoperative outcomes of surgical resected lung cancer patients, using preoperative CT for lung cancer staging. We also took in consideration the impact of sarcopenia on the national health cost and five years overall survival rate.

**Methods:** Patients affected by NSCLC, stage I–IIIa, undergoing radical surgery with a mediastinal lymphadenectomy, were enrolled. Forty-two patients were considered suitable for the study, according to the inclusion and exclusion criteria. Among them, 28 were male and 14 female with average age of 72 years. The identification of Sarcopenia status was reached with the use of computed tomography (CT), with two slices at the level of the third lumbar level (L3), allowing the measure of the cross-sectional area from L3 to the iliac crest, expressed in cm<sup>2</sup>. We identified sarcopenic and non-sarcopenic patients, using the Sarcopenia Index.

**Results:** Of the 42 patients suitable for the study, 13 were sarcopenic (31%) and 29 were non-sarcopenic (69%). Days of hospitalizations are 10 days in sarcopenic patients and 8.5 days in non-sarcopenic patients. Duration of permanence of the thoracic drainage is 7 days in sarcopenic patients and 5 days in non-sarcopenic patients. This is related with increased healthcare costs for sarcopenic patients (statistically significant:  $P < 0.0037$ ). The five-year survival rate was 57% in patients with sarcopenia and 88% in those without ( $P < 0.002$ ).

**Conclusions:** Our study demonstrates the impact of sarcopenia in different ambits, from the clinical outcomes to the health expenditure. Preventing the insurgence of sarcopenia is essential to improve the postoperative outcomes, and for the Health System, to reduce healthcare-related costs.

**Keywords:** Sarcopenia; non-small cell lung cancer (NSCLC); pulmonary surgery; health costs

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## Introduction

Lung cancer is the leading cause of cancer death in several countries, in particular non-small cell lung cancer (NSCLC) accounts for about 75–80% of primary lung cancer (1,2). Surgical resection is a potentially curative

treatment for NSCLC, but recurrence could develop in 27–38% of patients after surgical resection of stage I NSCLC (3). Tumor-specific factors, such as tumor size, node, and metastasis (TNM staging system) are important to determinate the postoperative prognosis (4). However,

physical factors, such as body mass index and sarcopenia, are also important for postoperative prognosis (5-7). Sarcopenia is a physical component of cachexia syndrome, characterized by significant loss of skeletal muscle mass and function. Furthermore, it is associated with poor quality of life, a risk of adverse outcomes, such as physical disability, and death (8).

For this reasons, sarcopenia is identified as a prognostic factor for various cancers, especially lung and colo-rectal cancer (9-11). In fact, a reduction of the skeletal muscle mass can be reflected on a loss of respiratory muscle mass and strength. The importance of this condition is more relevant when the diaphragm muscle is affected. Determination of sarcopenia can be achieved using various imaging techniques to assess skeletal muscle mass, such as computed tomography (CT), dual X-ray absorptiometry (DEXA), magnetic resonance imaging (MRI) and bio-impedance analysis (BIA) (8,12,13). In particular, CT scan has become a routine diagnostic tool for lung cancer staging and some authors have evaluated the depletion of muscle mass in various cancers, using this radiological technique (9-11). Measuring psoas muscle index (PMI) at the third lumbar level on CT was proposed for assessing the skeletal muscle mass (13). It is a convenient and inexpensive method that could be used in routine practice.

People with an active cancer have a reduced amount of lean body mass while fat mass is stable or increased (sarcopenic obesity) (9). Sarcopenia has been correlated with NSCLC by different studies, which has shown a reduction of the global survivor rate of sarcopenic patients who undergo thoracic surgery (14).

We conducted a retrospective study to investigate the link between sarcopenia and postoperative outcomes of surgical resected lung cancer patients, using preoperative CT for lung cancer staging. We also took in consideration the impact of sarcopenia on the national health cost and five years overall survival rate.

## Methods

Patients affected by NSCLC, stage I-IIIa, undergoing radical surgery, including lobectomy and bi-lobectomy, with a mediastinal lymphadenectomy, were enrolled. All surgical procedures were performed between 2002 and 2012 at University Campus Bio-Medico of Rome (UCBM). We excluded other types of cancer or synchronous cancer with a non-pulmonary primitivity, metastatic disease, stage IV or patients with a severe obesity ( $BMI > 30 \text{ kg/m}^2$ ).

Forty-two patients were considered suitable for the study, according to the inclusion and exclusion criteria. Among them, 28 were male and 14 females with average age of 72 years.

We performed the surgical procedures with the patient under general anaesthesia with lateral thoracotomy access (open surgery). We inserted two drainages into the pleural cavity, apical drainage for any air leaks, basal drainage for the fluid leaks.

The Ethics Committee of Campus Bio-Medico University of Rome approved this study (No: 882017).

## Measurements

The identification of Sarcopenia status was reached with the use of CT, with two slices at the level of the third lumbar level (L3), allowing the measure of the cross-sectional area from L3 to the iliac crest, expressed in  $\text{cm}^2$ . The anatomic section includes the following muscles: psoas, para-vertebral, intercostal, oblique, transverses and rectus. Using Software Osirix and *Hounsfield Units's* window, variables among patients were between  $-5$ – $150 \text{ HU}$  on average (range:  $-40/40$ – $150 \text{ HU}$ ).

We identified sarcopenic and non-sarcopenic patients, using the Sarcopenia Index, obtained from dividing the area find with the CT scan measuring, by the patient's height ( $\text{cm}^2/\text{m}^2$ ),  $52.4 \text{ cm}^2/\text{m}^2$  for the man and  $38.5 \text{ cm}^2/\text{m}^2$  for the woman.

We collected clinical parameters, including age, sex, weight (kg), height (cm), and BMI ( $\text{kg/m}^2$ ), glycemia (mg/dL) and arterial blood gases (ABG). The last two parameters were measured in two different conditions: pre operation, in the first and second postoperative day.

Finally, the evaluation of the infective risk and the health expenditure included the analysis of days of hospitalizations, duration of permanence of thoracic drainages, both apical and basal, expressed in days.

The result was considered statistically significant at the significance level of  $P < 0.05$ . Survival curves were constructed using Kaplan-Meier method and overall survival rates were compared using log-rank test.

## Results

Of the 42 patients suitable for the study, 13 were sarcopenic (31%) and 29 were non-sarcopenic (69%). Of the 13-sarcopenic patient, 9 were male and 4 females. We collected the median value of the parameters. BMI

**Table 1** Results of sarcopenic patients versus non sarcopenic patients

Variables	Sarcopenic	Non sarcopenic
Number of patients (%)	13 (31%)	29 (69%)
Age (median)	77	69
Sex		
Male (%)	9 (32%)	19 (68%)
Female (%)	4 (29%)	10 (71%)
BMI (kg/m <sup>2</sup> )	24.4	27.3
Days of hospitalizations (dd) (median)	10	8.5
Permanence of apical drainage (dd) (median)	4	4
Permanence of basal drainage (dd) (median)	7	5
AGB I postoperative day		
pO <sub>2</sub> (mmHg) (median)	74.4	87.3
pCO <sub>2</sub> (mmHg) (median)	40.25	40
SO <sub>2</sub> (%) (median)	95.75	97.1
AGB II postoperative day		
pO <sub>2</sub> (mmHg) (median)	72.9	79.4
pCO <sub>2</sub> (mmHg) (median)	36.9	37.6
SO <sub>2</sub> (%) (median)	96.3	97.6
Glycemia (mg/dL)		
Preoperative (median)	105	101
Postoperative (median)	132	113

is 24.4 kg/m<sup>2</sup> on sarcopenic patients and 27.3 kg/m<sup>2</sup> on non-sarcopenic patients. Days of hospitalizations are 10 days in sarcopenic patients and 8.5 days in non-sarcopenic patients. Duration of permanence of the thoracic drainage is 7 days in sarcopenic patients and 5 days in non-sarcopenic patients.

The AGB in the first postoperative day showed: pO<sub>2</sub> =74.4 mmHg, pCO<sub>2</sub> =40.25 mmHg, SO<sub>2</sub> =95.75% in sarcopenic patients and pO<sub>2</sub> =87.3 mmHg, pCO<sub>2</sub> =40 mmHg, SO<sub>2</sub> =97.1% in non-sarcopenic patients. The AGB in the second postoperative day showed: pO<sub>2</sub> =72.9 mmHg, pCO<sub>2</sub> =36.9 mmHg, SO<sub>2</sub> =96.3% in sarcopenic patients and pO<sub>2</sub> =79.4 mmHg, pCO<sub>2</sub> =37.6 mmHg, SO<sub>2</sub> =97.6% in non-sarcopenic patients.

Preoperative glycemia is 105 mg/dL in sarcopenic

patients and 101 mg/dL in non-sarcopenic patients while postoperative glycemia is 132 mg/dL in sarcopenic patients and 113 mg/dL in non-sarcopenic patients (*Table 1*).

Regarding the costs and the established reimbursement given to the UCBM between 2002–2012, on average, the care of a patient with NSCLC who underwent surgery for lobectomy and lymphadenectomy, amounted to 4,187 euro for non sarcopenic patients while, the same procedure, for a sarcopenic patient is about 5,686.75 euro (difference of 1,499.75 euro). This gap is due to 1.5 days of hospitalization more of non-sarcopenic patients than non-sarcopenic ones (10 *vs.* 8.5 days). We obtained the increase in health care spending, multiplying this value, 1.5, by the following costs: bed place (842 euro per day), geriatric counselling (65 euro each counselling), and blood tests (34 euro per day). The national health system refunded 8,067 euro for lung lobectomy hospitalization, so the UCBM received 3,880 euro (euro 8,067–4,187) for each non sarcopenic patient, while, because of the higher cost for the care, they received 2,380.25 euro (euro 8,067–5,686.75) for each sarcopenic patient (*Tables 2–4*).

The five-year survival rate was 57% in patients with sarcopenia and 88% in those without. Multivariate analysis revealed that sarcopenia was an independent unfavourable prognostic factor ( $P<0.002$ ) (*Figure 1*).

## Discussion

Basing on GLISTEN Study (15), there is a high prevalence of sarcopenia in the Italian population.

In our study, we focused on the role of sarcopenia in patients with NSCLC as an influential factor for the patient's outcome.

First of all, the healthcare costs are higher among sarcopenic patients (statistically significant:  $P<0.0037$ ).

Concerning the permanence of thoracic drainages, the apical drainage has the same permanence (4 days) in both sarcopenic and non-sarcopenic patients, while the basal drainage has a longer permanence in sarcopenic patients (7 *vs.* 5 days; statistically significant:  $P<0.0043$ ).

The longer permanence of the basal drainage could lead to infections: one of the major complications related to the drainage. Previous studies demonstrated that another condition could increase the risk of pulmonary complication and infections: the aging-related weakness of the diaphragm muscle due to atrophy of fast muscle fibers (type IIx and/or IIb) (16). Health expenditure could be burdened by the development of an infective

**Table 2** Health costs regarding a hospitalization for lung lobectomy in a non-specific patient

Cost type	Cost detail	Value (€)
Proceeds from discharge	Proceeds from DRG	8,067.00
Cost		4,187.42
Acceptance	Per discharge	9.40
Medical records	Per discharge	23.10
Meals	Per day of hospitalization (no ICU)	80.50
Prosthetic materials	Total	23.58
	Materials nursing department	0.78
	Materials operating room	22.80
Drugs	All	538.53
	Nursing department	75.57
Health care	Total	628.27
	Analysis laboratory	243.38
	Pathological anatomy	155.10
	Radiology	77.45
	Anaesthesia and pain therapy	13.63
	Cardiology	32.28
	Haematology	13.63
	Geriatrics	64.56
	Lab-haematology	28.24
Other materials		233.3
Garrisons		1,563
Chancellery		4.14
Laboratory materials		35.3
Haemocomponents	Haemocomponents	136.33
Waste disposal	Per hospitalization	205.00
Laundry	Per day of hospitalization (no ICU)	138.00
Bed place	Per day of hospitalization SSN (no ICU)	704.00

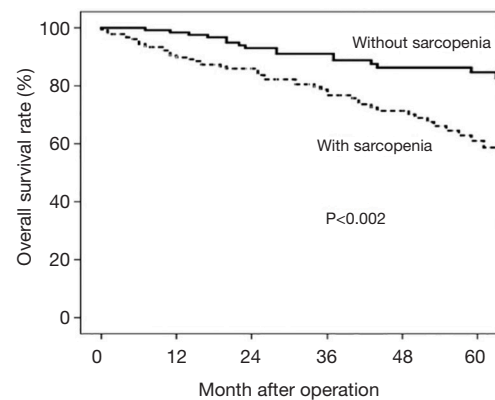
complication and the consequent necessity of counselling, tests, and prolonged hospitalization. On the other hand, both conditions can exasperate patients' outcome. Then we analysed the respiratory parameters ( $pO_2$ ,  $pCO_2$  and

**Table 3** Additional health costs for sarcopenic patients with a duration of hospitalization greater than 1.5 days compared with non-sarcopenic patients

Health care	Additional health costs for sarcopenic patients
Meals	(Euro) $80.5 \times 1.5$ (days) = 120.75 euro
Bed place	(Euro) $842 \times 1.5$ (days) = 1,263 euro
Analysis laboratory	(Euro) $34 \times 1.5$ (days) = 51 euro
Geriatrics counselling	65 euro
Total $\times 1.5$ days	1,499.75 euro

**Table 4** Proceeds/cost ratio per each hospitalization of sarcopenic patients versus non sarcopenic patients undergoing lung lobectomy

Variable	Outcome
DRG 75-National Health System Refund	8,067 euro
UCBM cost for non-sarcopenic patient	4,187 euro
UCBM proceeds for non-sarcopenic patient	$8,067 - 4,187 = 3,880$ euro
UCBM cost for sarcopenic patient	$4,187 + 1,499.75 = 5,686.75$ euro
UCBM proceeds for sarcopenic patient	$8,067 - 5,686.75 = 2,380.25$ euro

**Figure 1** Five-year survival rate.

$SO_2$ ) in the first and second postoperative days. The values found are similar in the two groups, but sarcopenic patients showed a slower recovery of the normal range (not statistically significant:  $P < 0.21$ ). This agrees with the

negative effect of sarcopenia on the lung function and ventilation mechanism.

At last, the glycaemic median (mg/dL) is higher in sarcopenic patients than in non sarcopenic, both in preoperative (105 *vs.* 101) and postoperative (132 *vs.* 113), favouring a condition of insulin-resistance in sarcopenic patients (statistically significant: preoperative  $P < 0.0002$ ; postoperative  $P < 0.0001$ ). In these patients, it takes place a down-regulation of anabolic pathways such as IGF-1 and androgen (15,16). The high glycaemic level induced the loss of muscle mass and the development of sarcopenia. Different mechanisms act in this process, and, most of them, are due to the inflammation (17,18). People with metabolic syndrome, insulin-resistance, or type 2 diabetes have an increased level of adipokines (TNF $\alpha$ , IL6), inflammatory cytokines correlated with muscle mass loss. Resistin levels are increased too, which has an anti-myogenic effect activating the NF $\kappa$ B pathway and altering the metabolism of the muscle (18). Local inflammation reprograms the skeletal muscle transcriptome leading to altered expression of pro-inflammatory and pro-fibrotic genes (19).

High blood content of TNF- $\alpha$ , during cachexia, increases muscle cell apoptosis; AGEs change the bones, muscles and vessels structure because of the production of IL-6.

Other studies demonstrated the association between sarcopenia, malnutrition and inflammation markers. A harmful diet, with a high intake of fatty meals, can even affect our mitochondria.

On one side, it has been demonstrated what the positive effect of supplementation of the diet with protein, calories, amino-acids, and vitamin D as well as physical exercise can reduce on the loss of muscle mass (20). The level of inflammatory marker (IL6 and TNF $\alpha$ ) is inversely proportional with the albumin level, so a normalization of the protein level, especially in the post-operative, could reduce inflammation (21).

On the other side, some studies provided the beneficial impact of AIDs (non-selective Cox and selective Cox-2 inhibitors) on performance and muscle weakness, reducing the grade inflammation. For example: piroxicam decreases the baseline values in IL-6, while celecoxib showed a significant decrease in IL-10 (17). As different studies underline, pro-inflammatory cytokine IL-6 has a role in cachexia and cancer growth, up to consider the target therapy against IL-6 as anti-tumour and useful for the treatment of the muscle loss (17-21).

In conclusion, our study demonstrates the impact of

sarcopenia in different ambits, from the clinical outcomes to the health expenditure. Sarcopenia, the “big geriatric syndrome”, lead with her the development of a set of comorbidities that makes the care of these patients difficult.

A possible treatment to prevent and relieve the effect of sarcopenia can be physical exercise, diet and anti-inflammatory drugs.

Preventing the insurgence of sarcopenia is therefore essential, creating protocol of physical activity, diet and therapy aimed at reducing the loss of strength and muscle mass that physiologically decrease with the age. This is fundamental for the patients, to improve the postoperative outcomes, and for the Health System, to reduce healthcare-related costs.

Naturally, these data need to be confirmed in a more powerful study, and the economic impact of these patients recorded outcomes should be investigated as well.

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## Footnote

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/jhmhp.2019.08.04>). The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Informed consent was waived due to the retrospective nature of the study. The Ethics Committee of Campus Bio-Medico University of Rome approved this study (No: 882017).

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