Prevalence of sarcopenia in chronic obstructive patients hospitalized in pneumology at the CHU of Clermont-Ferrand

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UFR DE MÉDECINE
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Summary

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Abbreviations list

BMI: body mass index

COPD: chronic obstructive pulmonary disease

CRP: C-reactive protein

DEXA: Dual-energy X-ray absorptiometry

EWGSOP: European Working Group on Sarcopenia in Older People

FEV1: forced expiratory volume in one second

FFMI: fat-free mass index

FVC: forced vital capacity

HOMA-IR: homeostatic model assessment insulin resistance

MIP: maximal inspiratory pressure

SMI: skeletal muscle mass index

Abstract

Background. COPD is characterized by a loss of skeletal muscle mass. Associated with a decrease in physical performance, it defines sarcopenia. The objective of this study is to describe the prevalence of sarcopenia in patients with chronic obstructive pulmonary insufficiency during hospitalization for acute exacerbation. The evolution of sarcopenia at six months and the survival at one year of these patients were also studied.

Methods. We prospectively included hospitalized patients and measured their body composition, handgrip strength and respiratory function, including maximum inspiratory pressure (MIP) representative of diaphragmatic function. The same measurements were performed at six months in consultation. Sarcopenia was defined by a low skeletal muscle mass index (SMI) measured by body impedance analysis, and a decreased handgrip strength (HGS), based on the criteria of the European Working Group on Sarcopenia in Older Adults (EWGSOP). Survival data were collected eighteen months after hospitalization.

Results. We analyzed data from fifty-four patients, aged 68 ± 9 years and BMI 26.9 ± 7.8 kg/m^2, with an average FEV1 of 1.13 ± 0.49 L (45 ± 16%). Sarcopenia was observed in 48% of patients during hospitalization and in 30% of patients in consultation. At six months, the SMI improved more for men than women (+5% vs -3%, p = 0.01), it tends to improve more for patients taking oral nutritional supplements (+13% vs +1%, p = 0.05). HGS tends to increase more in physically active patients (+324% vs. +7%, p = 0.05). In multivariate analysis, SMI and MIP were linked (p = 0.03). The one-year survival rate was lower in sarcopenic patients (65% vs. 86%, p = 0.03).

Conclusion. Sarcopenia in chronic obstructive pulmonary insufficiency is prevalent during exacerbation and in a stable state. It exposes to lower survival. A multimodal management reduces its prevalence.

Key words: Body composition, Chronic obstructive pulmonary disease, COPD, Malnutrition, Mortality, Nutritional assessment, Prevalence, Sarcopenia.

I. Introduction

Fifth cause of death in 2015 (1) and soon third in 2030 according to World Health Organization (2), chronic obstructive pulmonary disease (COPD) has recently been recognized “public health emergency” in France. As a consequence of a smoking history, the prevalence of COPD and the hospitalizations for acute exacerbations is increasing (3,4), especially among the elderly.

This population is at risk of age-related malnutrition (anorexia, anabolic defect, sedentary lifestyle) and respiratory disorders (dyspnea interfering with food intake, hypermetabolism through increased ventilatory work, systemic inflammation). The aging of the population involves taking an interest in its determinants of health. Combination of genetic and environmental factors, sarcopenia (loss of muscle mass especially at the skeletal level) is one of these determinants.

Loss of body weight or muscle mass is a significant event in the evolution of COPD because of its association with premature mortality, poor functional status and quality of life (5,6). Sarcopenia is a health problem representative of frailty, loss of autonomy (7,8) and decreased muscle strength (9,10). Its prevalence is high in many organ pathologies such as COPD (11), but remains little studied in acute respiratory failure. The frequency and evolution of sarcopenia is unknown in chronic obstructive patients after an acute exacerbation, as well as the role of systemic inflammation on body composition.

Metabolic phenotypes have been defined to stratify patients’ nutritional risk in COPD (12). Hospitalizations could be considered an opportunity for nutritional assessment, patient counselling and implementation of longer-term nutritional management. As a result, improving the nutritional status of these patients could influence their respiratory function. Conversely, does the improvement in respiratory mechanics lead to a change in body composition?

Through this study, we describe the prevalence of sarcopenia in hospitalized chronic obstructive patients for acute exacerbation and at six months from it, we verify the hypothesis that sarcopenia may affect patients’ lung function and we study the survival rate of sarcopenic patients.

II. Methods and materials

This is a French observational descriptive and analytical study, monocentric in the Gabriel-Montpied University Hospital of Clermont-Ferrand. Recruitment was done in the Pneumology Department between 1st of January and 1st of May 2017. 54 patients participated in a prospective survey of sarcopenia and hospitalization risks.

Inclusion criteria were: age ≥ 18 years, a history of persistent airflow obstruction (a post-bronchodilator forced expiratory volume in one second (FEV1) – forced vital capacity (FVC) ratio less than 0.7 of the predicted value after 400 µg of inhaled salbutamol) (13,14) compatible with respiratory function tests (FEV1 increased less than 12% and 200 mL after bronchodilation, according to the GOLD definition) (15), and informed consent to examination of nutritional status.

Exclusion criteria were: bronchopulmonary cancer being treated, disabling rheumatic disease, recent stroke or surgery (less than three months), missing data on essential variables (body mass index (BMI), mid-arm muscle circumference, impedancemetry). Patients with bronchopulmonary cancer were excluded because of a major impact on nutritional status. Exercise capacity would have been influenced by a disabling rheumatic disease, a recent stroke or surgery.

On a weekly basis, we included patients with known persistent airflow obstruction, consecutively hospitalized in Gabriel-Montpied University Hospital's Pneumology Department. We offered to participate a study involving complementary nutritional tests (recommended by national and international authorities (16–18) to their standard respiratory management), and a six months' follow-up consultation in stable clinical condition: examination and surveys, mid-arm muscle circumference, impedancemetry, spirometry. The initial evaluation was performed on average 3.6 days after the patient entered the Pneumology department.

This observational study was approved by the French "Commission Nationale Informatique et Libertés", and all patients gave their verbal and written informed consent for their participation (Appendix I).

The Ethics Committee of the Gabriel-Montpied University Hospital approved the research protocol. The study was registered at clinicaltrials.gov (NCT03111849).

Definition of sarcopenia

Skeletal muscle mass was calculated using an impedance equation to predict appendicular skeletal muscle mass: [0.401 x (height^2/resistance) + (3.825 x gender) - (0.071 x age) + 5.102], where height is in cm; resistance is in ohms; for sex, men = 1 and women = 0; and age is in years (19). Skeletal muscle mass index (SMI) was calculated as the absolute skeletal muscle mass divided by height squared (kg/m^2). An SMI lower than 8.87 kg/m^2 for men and 6.42 kg/m^2 for women was considered abnormal. Muscle strength was decreased if men's handgrip was lower than 30 kg and women lower than 20 kg (20). Sarcopenia was defined as the presence of low skeletal muscle mass with low handgrip strength (21). Undernutrition was defined with the criteria of the Haute Autorité de Santé (HAS) 2007 (22).

Respiratory parameters

The following variables, which are known to predict outcome in chronic obstructive diseases, were evaluated and recorded at the time of enrolment and during the follow-up consultation.

We used three questionnaires (Appendix II) to assess the degree of dyspnea by the modified Medical Research Council (mMRC) scale (23), the level of physical exercise and smoking habits (three categories: non-smokers, active smokers and ex-smokers defined by a tobacco cessation for at least three months). Physiotherapy and rehabilitation course in the last six months were recorded. A six-minute-walk test was performed according to American Thoracic Society (ATS) recommendations (24) to measure functional status of patients and skeletal muscle endurance, as a predictor of morbidity and mortality (25), using a theoretical calculated value provided by Enright and Sherill (26,27).

We chose this test among others because it is the most used in Pneumology to assess exercise capacity. Respiratory function tests were done using a Jaegger 920 MasterLab1 spirometer and Body Box (both Masterlab, Jaegger, Würzburg, Germany) along with the European Community for Steel and Coal guidelines to establish predicted values (28,29). We determined FEV1, FVC, the functional residual capacity, the inspiratory capacity and total lung capacity (30,31), the maximum inspiratory and expiratory pressures and the sniff nasal inspiratory pressure (32). A composite prognostic index, the BODE index, was calculated as surrogate of global disease severity (33). Arterial blood gases data were collected.

Nutritional assessment

We measured weight (to within 0.5 kg) and height (to within 0.5 cm) to calculate BMI (34), waist and hip circumference (to within 0.5 cm). The mid-arm muscle circumference of the dominant side (to within 0.5 cm, reflects of muscle protein), associated with the triceps skinfold (to within 0.2 mm, indicates the calorie reserves stored in the form of fat, average of the three values varying by less than 1 mm), were evaluated to estimate muscle mass (mid-arm muscle area[1]) (35). Although this is not the most precise method, it has an important interest in medical practice because it allows an appreciation of the evolution of muscle mass during a clinical situation. For the measurement of the skeletal muscle strength, we used the hydraulic Jamar's dynamometer (36) in the second position (the most used), three times with the dominant hand (37) to do the average of the two best values (to within 1 kg). This test has an excellent reproducibility (38) and inter-rater reliability (39) using standardized instructions. The bioelectrical impedance measurement (Bodystat Quadscan 4000 Ltd, Isle of Man, UK) was carried out in accordance with the European Society for Clinical Nutrition and Metabolism (ESPEN) recommendations (40,41). Subjects were measured for height and weight at the time of the impedance measurement. This method has the advantages to be inexpensive, portable, simple, safe,

[1] Mid-arm muscle area was calculated by the following equation:
(mid-arm circumference [cm] – 3.14 x tricipital skin fold thickness [mm])^2 / (4 x 3.14)

quick, noninvasive (42,43) and is valid in COPD patients (44,45) to measure the fat-free mass index (FFMI). FFMI was calculated by dividing fat-free mass by height squared.

Involuntary weight loss over the past six months, use of oral nutritional supplements and recent enteral or parenteral nutrition were recorded. Due to limitations in memory, the reliability of information generally decreases with the length of the period surveyed, so that we limited the questions to six months. We evaluated the food intake via a verbal and visual scale, asking "Can you indicate the quantities you are currently eating, placing the cursor between 0 meaning "nothing at all" and 10 meaning "as usual"? This scale is statistically correlated with calculated energy intake, especially in undernourished patients (46). Insulin resistance was assessed with the calculation of the Homeostatic Model Assessment (HOMA) index, using the formula: fasting serum insulin (mU/L) × fasting plasma glucose (mmol/L)/22.5 (47).

Statistical analysis

Data were expressed as frequencies and associated percentages for categorical data, as mean ± standard deviation (or as median and interquartile range when data were not normally distributed) for quantitative parameters. Normality was assessed graphically and using Shapiro-Wilk's test.

Comparisons between two groups were done using Chi-squared test (or Fisher's exact test when appropriate) for categorical data and using Student's t-test (or Mann & Whitney test when data not normal) for continuous data.

Univariate analysis was used to study the factors associated with SMI and handgrip strength improvement. Maximal inspiratory pressure (MIP) was analyzed in a multivariate mixed model (taking the patient as random effect), adjusted on SMI (or FFMI), functional residual capacity and time in order to assess relationship between SMI (or FFMI) and MIP with controlled functional residual capacity. Results are expressed as regression coefficients and their 95% confidence interval. To compare muscle

mass measurements, we used Pearson (or Spearman when data were not normal) correlation coefficients.

Intragroup evolution was analyzed using Student's paired test. Survival analysis was performed, from discharge until 18 months later or death when it occurred. Survival curves were plotted using Kaplan Meier method and sarcopenic versus non-sarcopenic groups were compared using log rank test.

All tests were two-sided and a p value < 0.05 was considered statistically significant. Statistics were computed with Stata v12 (Stata Corp, College Station, Texas, USA).

III. Results

This study consecutively included 58 patients with all degrees of severity of airflow obstruction. We excluded four non-obstructive phenotypes (three restrictive and one sleep apnea syndrome). 54 patients were evaluated at inclusion and 30 at six-month's follow-up (Flow chart in Appendix III). All patients were Caucasians. Patients lost to follow-up were not statistically different from others, particularly with respect to age, gender and skeletal muscle index (SMI).

Prevalence of sarcopenia

The prevalence of sarcopenia was 48% (26/54 patients, Figure 1). The mean low SMI and handgrip strength was respectively 7.01 kg/m^2 and 20.3 kg for men, 5.38 kg/m^2 and 13.7 kg for women (no difference by gender for SMI, p = 0.15 and handgrip strength, p = 0.22). The characteristics of sarcopenic patients are presented in Table I. Sarcopenic patients were significantly older and more anemic, they had lower weight and fat-free mass index (FFMI). FVC, FEV1, functional residual capacity and diffusing capacity were not influenced by sarcopenia but maximal inspiratory and expiratory pressures were lower (p = 0.01 and 0.009 respectively). The FFMI of patients with edema of the lower limbs was increased compared to patients without edema (mean 22.9 kg/m^2 versus 16.0 kg/m^2 p = 0.06).

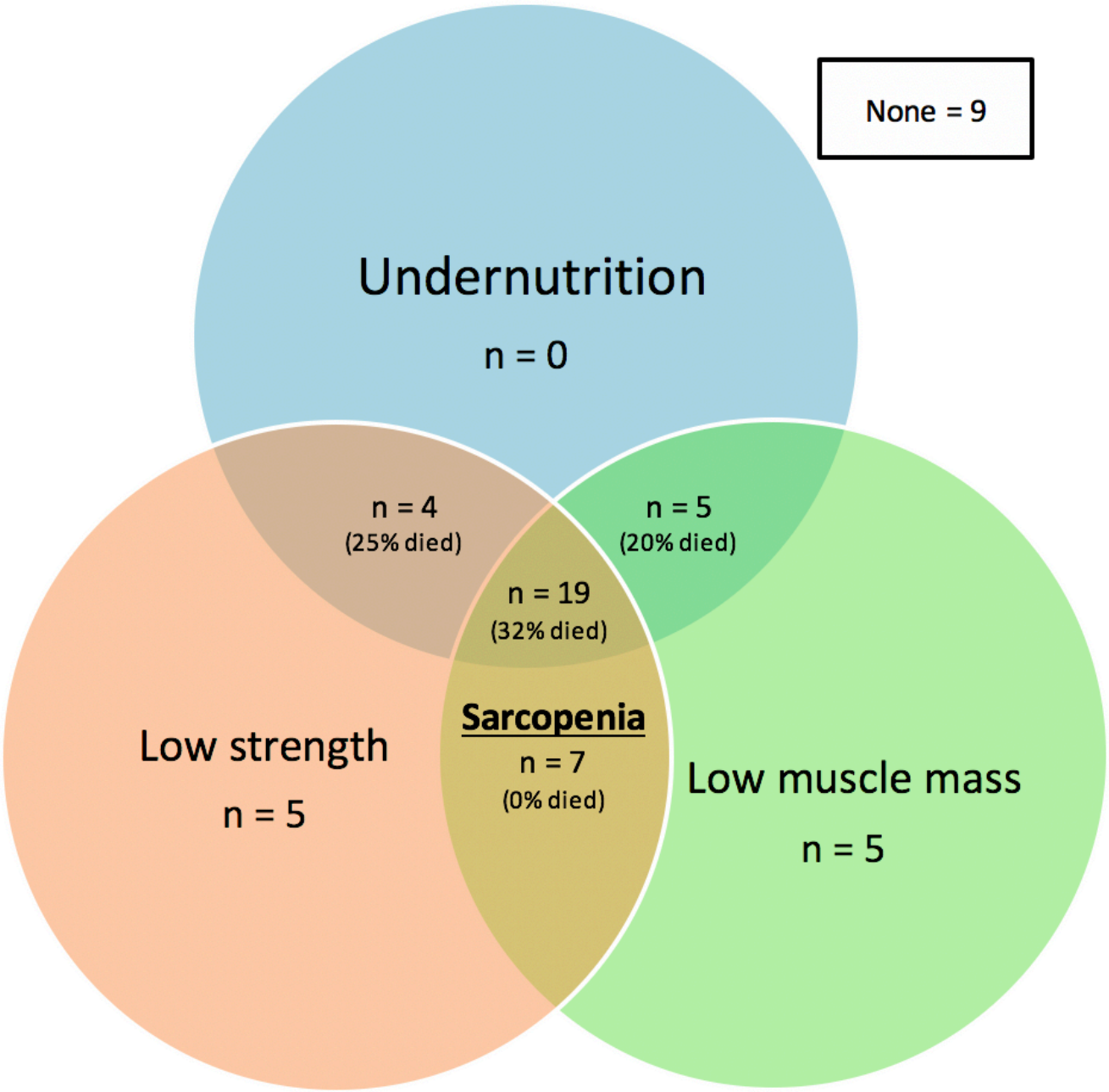

FIGURE 1. Prevalence of sarcopenia and undernutrition among 54 hospitalized patients with persistent airflow obstruction

Sarcopenia is defined as low handgrip strength and low skeletal muscle mass, corresponding to 26 patients (7 + 19). Undernutrition is defined by recent weight loss or low BMI or low albumin and applies to 28 patients (4 + 5 + 19). All deceased patients were undernourished.

TABLE I. Baseline characteristics of the first 54 patients included				
Characteristics	Sarcopenic patients (n = 26)	Non-sarcopenic patients (n = 28)	Total (n = 54)	p value
	Mean ± SD			
Age (year)	72 ± 9	63 ± 11	68 ± 9	**0.003**
Men (No. and %)	18 (69%)	19 (68%)	37 (69%)	0.91
Chronic respiratory insufficiency (No. and %)	9 (35%)	14 (50%)	23 (43%)	0.25
Respiratory features				
Respiratory kinesitherapy before (No. and %)	9 (35%)	3 (11%)	12 (22%)	**0.04**
Recent pulmonary rehabilitation (No. and %)	3 (12%)	3 (11%)	6 (11%)	1
mMRC dyspnea scale*	3.1 ± 1.2	2.8 ± 1.4	2.9 ± 1.3	0.35
Physical activity (No. and %) $	8 (31%)	5 (18%)	13 (24%)	0.27
Smoking history (years)	39 ± 13	39 ± 11	39 ± 12	0.96
Smoking history (pack-year)	43 ± 22	50 ± 27	47 ± 25	0.36
Distance walked in six min (m)	161 ± 111	217 ± 111	191 ± 113	0.10
Hypercapnia (mmHg)	45 ± 10	51 ± 11	48 ± 11	**0.04**
Haemoglobin (g/dL)	12.4 ± 2.1	14.4 ± 2.2	13.4 ± 2.4	**0.002**
FVC (L)	2.20 ± 0.86	2.36 ± 0.88	2.29 ± 0.87	0.50
FVC (% predicted)	74 ± 18	70 ± 23	72 ± 21	0.50
FEV1 (L)	1.03 ± 0.37	1.22 ± 0.56	1.13 ± 0.49	0.16
FEV1 (% predicted)	45 ± 11	46 ± 20	45 ± 16	0.86
Functional residual capacity (% predicted)	160 ± 35	157 ± 44	158 ± 40	0.78
Diffusing capacity (% predicted)	52 ± 22	59 ± 30	56 ± 27	0.43
MIP (cm H2O)	35 ± 17	49 ± 19	43 ± 19	**0.01**
Maximal expiratory pressure (cm H2O)	65 ± 26	93 ± 39	81 ± 37	**0.009**
Sniff nasal inspiratory pressure (cm H2O)	49 ± 22	56 ± 21	53 ± 22	0.26
GOLD I - II - III - IV (%)	0 - 39 - 17 - 43	4 - 36 - 11 - 50	2 - 37 - 14 - 47	0.86
BODE index€	6.5 ± 2.0	5.3 ± 2.0	5.9 ± 2.1	0.08
Length of hospitalisation (days)	17.4 ± 13.0	15.6 ± 12.9	16.5 ± 12.9	0.60

Nutritional features				
Diabetic (No. and %)	6 (23%)	8 (29%)	14 (26%)	0.65
Six months' weight loss (%)	3.9 ± 12.9	1.8 ± 9.4	2.8 ± 11.2	0.62
ONS before hospitalization (No. and %)	8 (31%)	2 (7%)	10 (19%)	**0.04**
ONS during hospitalization (No. and %)	8 (31%)	3 (11%)	11 (20%)	0.07
Recent artificial nutrition (No. and %)	3 (12%)	0 (0%)	3 (6%)	0.11
EFI scale£	6.4 ± 3.0	7.3 ± 2.9	6.9 ± 3.0	0.24
Weight (kg)	60.5 ± 16.4	85.6 ± 21.6	73.5 ± 22.9	**< 0.001**
BMI (kg/m^2)	22.5 ± 5.0	30.9 ± 7.8	26.9 ± 7.8	**< 0.001**
Waist/hip ratio	0.99 ± 0.07	1.02 ± 0.08	1.01 ± 0.08	0.06
Serum albumin (g/L)	33.3 ± 5.1	35.4 ± 4.8	34.4 ± 5.0	0.12
CRP (mg/L)	15.3 [6.7-38.7]	8.9 [1.8-17.1]	12.1 [6.1-26.5]	0.17
Fibrinogen (g/L)	5.4 ± 1.3	4.8 ± 1.0	5.1 ± 1.2	0.06
Fasting insulin (mUI/L)	13.3 ± 10.8	16.4 ± 10.0	15.0 ± 10.4	0.29
HOMA-IR	3.83 ± 5.41	4.45 ± 4.00	4.2 ± 4.7	0.64
Free testosterone (nmol/L)	5.98 ± 5.65	5.73 ± 4.26	5.9 ± 4.9	0.86
25-OH-vitamin D (ng/mL)	19.0 ± 14.0	11.8 ± 9.3	15.3 ± 12.3	**0.03**
Mid-arm muscle area (cm^2)	26.4 ± 12.4	32.2 ± 10.0	29.4 ± 11.5	0.06
FFMI (kg/m^2)	14.6 ± 4.2	20.5 ± 4.4	17.7 ± 5.2	**< 0.001**
Body fat mass index (kg/m^2)	8.0 ± 2.4	10.5 ± 5.4	9.3 ± 4.4	**0.03**
Phase angle (degrees)	4.4 ± 1.5	5.5 ± 1.1	5.0 ± 1.4	**0.004**

Abbreviation: GOLD = Global Initiative for Chronic Obstructive Lung Disease; ONS = oral nutritional supplement

* Scores on the modified Medical Research Council (mMRC) dyspnea scale can range from 0 to 4, with a score of 4 indicating that the patient is too breathless to leave the house or becomes breathless when dressing or undressing.

$ A regular activity, as more than 30 minutes a day at least three times a week, is scored 1

€ Higher scores on the BMI, degree of airflow obstruction, dyspnea, and exercise capacity (BODE) index indicate a greater risk of death (Celli, 2004)

£ Evaluation of food intake (EFI), is a scale asking "Can you indicate the quantities you are currently eating, placing the cursor between 0 meaning "nothing at all" and 10 meaning "as usual"?

Respiratory parameters

Of the 54 patients with persistent airflow obstructions (severity presented in Table II), 50 had COPD, three had bronchial dilation and one had asthma-copd overlap (ACO). They were hospitalized for acute respiratory failure in 35 cases (65%), coming from emergency department (44%) or intensive care unit (26%). The number of patients with chronic respiratory insufficiency was 23 (43%). Of the 16 active smokers at inclusion, four have quit smoking for at least three months after the hospitalization.

During hospitalization, all patients had a six minutes' walk test shorter than the theoretical calculated value. The percentage of patients reporting regular physical activity increased from 24 to 45% with a change in behavior for seven patients. Active patients had significantly better improvement in walking perimeter at six months (improvement of 184 ± 103 meters vs 72 ± 71 meters, $p < 0.001$). One third of the patients were anemic with no change after six months.

The mean length of stay in Pneumology was 16.5 days and 80% of patients went home. After hospitalization, 12 patients underwent respiratory physiotherapy and six underwent a respiratory rehabilitation program in a specialized structure.

TABLE II. Respiratory characteristics of the 54 patients

Respiratory characteristics		No. of patients (%)
Airflow limitation severity*	GOLD I (FEV1 ≥ 80% predicted)	1 (2%)
	GOLD II (50% ≤ FEV1 < 80% predicted)	19 (37%)
	GOLD III (30% ≤ FEV1 < 50% predicted)	7 (14%)
	GOLD IV (FEV1 < 30% predicted)	24 (47%)
ABCD assessment tool$	GOLD C (mMRC 0-1)	8 (15%)
	GOLD D (mMRC ≥ 2)	46 (85%)
BODE index score€	BODE 0-2	2 (5%)
	BODE 3-4	9 (21%)
	BODE 5-6	15 (36%)
	BODE ≥ 7	16 (38%)

Abbreviation: GOLD = Global Initiative for Chronic Obstructive Lung Disease
* Three missing data
$ Classification according to the revised combined COPD assessment (GOLD 2017)
€ Higher scores on the BMI, degree of airflow obstruction, dyspnea, and exercise capacity (BODE) index indicate a greater risk of death (Celli, 2004). 12 missing data

Nutritional assessment

Undernutrition was found in 28 patients (among them, 11 were under 70 years, Figure 1). Mean patient weight was 73.5 ± 22.9 kg for a calculated mean BMI of 26.9 ± 7.8 kg/m^2. Nutritional phenotypes are presented in Table III, four patients were morbidly obese (BMI > 40 kg/m^2) and only one patient was sarcopenic obese (6% of obese patients). The number of patients who lost at least 10% of their weight in the past six months was 13 at baseline and none six months later.

Anorexia was defined as a score under seven on the food intake scale and was found in 43% patients at baseline (23/53, one missing data) and 17% (5/30) after six months. Patient appetite improved 1.9 points with 2.5 kg weight gain and 5.1 g/L albumin improvement. Two patients continued taking oral nutritional supplements and four stopped them after the hospitalization. At the time of exacerbation, patients had a low-grade systemic inflammation (mean fibrinogen 5.1 ± 1.2 g/L and CRP 23 ± 37 mg/L) with no significant decrease for both at six months ($p = 0.53$ and 0.99). Vitamin D was lower than 20 ng/mL (50 nmol/L) in 36 cases (67%) and increased significantly after six months (12.6 ± 8.9 ng/mL at baseline, 18.7 ± 10.5 ng/mL at six months, $p = 0.02$). Testosterone level was lower than norms (by gender and menopause) in 36 cases at baseline with no significant improvement. In the 40 non-diabetic patients (74%), HOMA index was higher than 2.5 in 56% of cases and did not change significantly after six months. For the 14 diabetic patients (26%), HOMA index was higher than 4.0 in 33% of cases initially, without data at six-month's follow-up.

We compared different methods of measuring muscle mass (Table IV), using appendicular skeletal muscle index (ASMI) obtained by DEXA (dual-energy X-ray absorptiometry) as reference. SMI and FFMI have a high Pearson's correlation coefficient ($r \geq 0.90$ $p < 0.001$), as well as mid-arm muscle area ($r = 0.84$ $p < 0.001$).

TABLE III. Nutritional phenotypes of the first 54 patients					
Characteristics (Men/women norm)	Underweight (BMI < 18.5) n = 9	Normal weight (18.5 ≤ BMI < 25) n = 15	Overweight (25 ≤ BMI < 30) n = 14	Obesity (BMI ≥ 30) n = 16	Total (% of men) n = 54 (69%)
Sarcopenia*	8	8	9	1	26 (69%)
Low SMI (< 8.87/6.42 kg/m^2)	9	14	11	2	36 (75%)
Low handgrip strength (< 30/20 kg)	8	8	12	7	35 (63%)
Undernutrition$	9	9	8	2	28 (68%)
Abdominal obesity (waist circumference ≥ 94/80 cm)	0	10	14	16	40 (68%)
Android obesity (waist/hip ratio > 1/0.85)	3	12	13	12	40 (60%)

Body mass index (BMI) is expressed in kg/m^2
* Sarcopenia was defined as the presence of low skeletal muscle mass index (SMI) with low handgrip strength
$ Undernutrition was defined with the criteria of the HAS 2007 (45)

TABLE IV. Comparison of muscle mass measurements at six months (n = 17)			
Variables	Pearson correlation coefficient r	R^2	p value
ASMI (kg/m^2)	-	-	-
SMI (kg/m^2)	0.94	0.89	< 0.001
FFMI (kg/m^2)	0.90	0.81	< 0.001
Mid-arm muscle area (cm^2)	0.84	0.70	< 0.001

Evolution of sarcopenia and respiratory function

Six months after hospitalization, sarcopenia was found in nine patients (30%). Sarcopenic patients didn't improve significantly their SMI and handgrip strength (Table V) but appetite was better of 2.1 ± 0.8 points on the appetite scale (p = 0.02) and serum albumin was higher of 5.5 ± 0.9 g/L (p < 0.001). Dyspnea decreased of 0.9 ± 0.3 points on mMRC scale (p = 0.02) and distance walked in six minutes improved of 109 ± 32 meters (p = 0.009). Figure 2 shows differences of evolution between sarcopenic and non-sarcopenic patients. Five patients (36%) recovered from sarcopenia by normalizing either their handgrip strength and/or their SMI, without significant amelioration of the respiratory and nutritional parameters between no-more-sarcopenic patients and still-sarcopenic patients (Table VI).

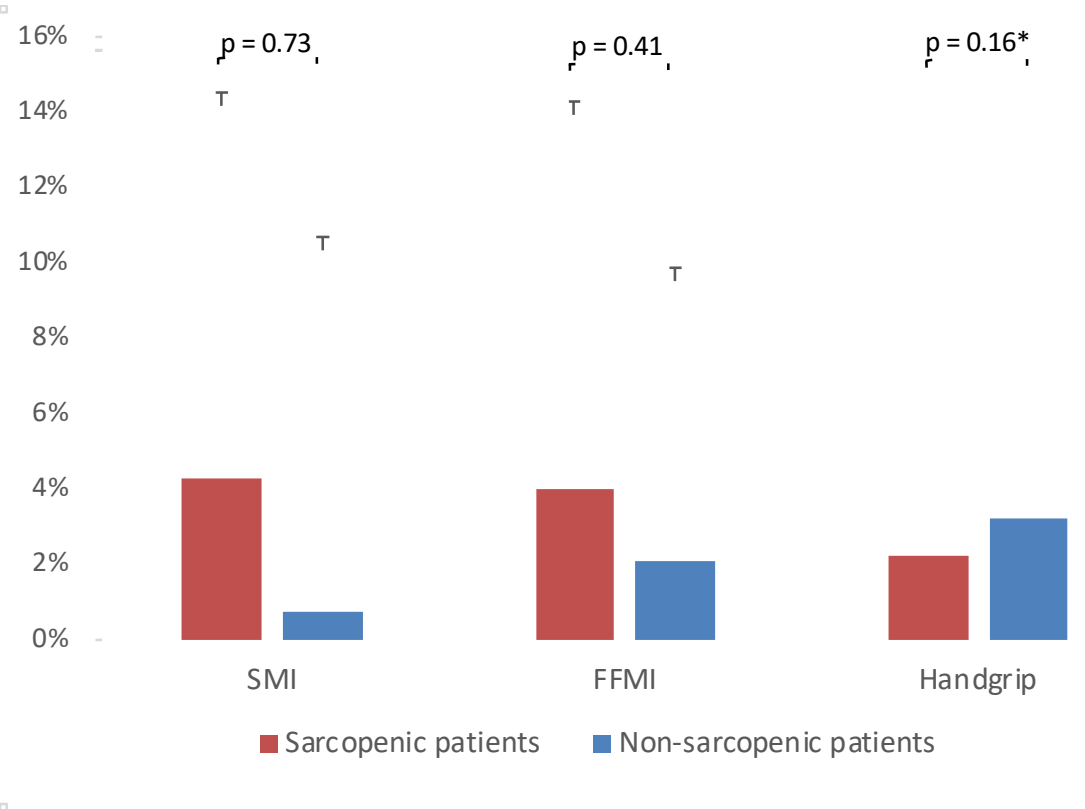

FIGURE 2. Improvement of sarcopenia determinants at six months

The figure shows the percentage improvement at six months of each parameter according to the initial sarcopenic status. Sarcopenic patients do not improve significantly more their muscle mass and handgrip strength than non-sarcopenic patients.
* The standard deviation was too large to be represented (628% influenced by one extreme value, and 22% respectively).

TABLE V. Improvement of the 14 sarcopenic patients followed at six months					
Characteristics	At baseline	At six months	Evolution	p	n missing value
SMI (kg/m^2)	6.6 ± 1.0	6.8 ± 1.1	+0.2 ± 0.2	0.24	0
Handgrip strength (kg)	17.9 ± 7.9	22.8 ± 6.4	+4.9 ± 2.7	0.09	0
Respiratory features					
mMRC dyspnea scale*	3.1 ± 1.4	2.1 ± 1.3	-0.9 ± 0.3	**0.02**	0
Distance walked in six min (m)	197 ± 117	306 ± 112	+109 ± 32	**0.009**	5
Haemoglobin (g/dL)	12.9 ± 2.2	13.2 ± 1.6	+0.3 ± 0.5	0.55	4
FVC (L)	2.59 ± 0.85	2.52 ± 0.78	-0.07 ± 0.13	0.60	3
FEV1 (L)	1.17 ± 0.34	1.08 ± 0.38	-0.09 ± 0.09	0.31	3
MIP (cm H2O)	42 ± 17	45 ± 23	+3 ± 4	0.50	6
Maximal expiratory pressure (cm H2O)	72 ± 27	71 ± 35	-1 ± 8	0.93	6
Sniff nasal inspiratory pressure (cm H2O)	58 ± 26	54 ± 18	-3 ± 6	0.59	6
BODE index€	5.7 ± 2.5	4.0 ± 2.6	-1.7 ± 1.0	0.14	7
Nutritional features					
EFI scale£	7.4 ± 2.5	9.5 ± 1.5	+2.1 ± 0.8	**0.02**	1
Weight (kg)	65.4 ± 14.6	67.0 ± 14.8	+1.7 ± 1.2	0.20	0
Serum albumin (g/L)	35.1 ± 4.7	40.6 ± 5.4	+5.5 ± 0.9	**< 0.001**	4
Mid-arm muscle area (cm^2)	29.8 ± 11.6	31.1 ± 8.9	+1.3 ± 2.1	0.53	0
FFMI (kg/m^2)	15.9 ± 2.8	16.5 ± 2.7	+0.7 ± 0.3	0.08	0
Body fat mass index (kg/m^2)	8.5 ± 2.9	8.2 ± 2.9	-0.3 ± 0.5	0.50	0
Phase angle (degrees)	4.8 ± 1.7	4.3 ± 0.8	-0.5 ± 0.3	0.15	0

* Scores on the modified Medical Research Council (mMRC) dyspnea scale can range from 0 to 4, with a score of 4 indicating that the patient is too breathless to leave the house or becomes breathless when dressing or undressing.

€ Higher scores on the BMI, degree of airflow obstruction, dyspnea, and exercise capacity (BODE) index indicate a greater risk of death (Celli, 2004)

£ Evaluation of food intake (EFI), is a scale asking "Can you indicate the quantities you are currently eating, placing the cursor between 0 meaning "nothing at all" and 10 meaning "as usual"?

TABLE VI. Study of the five patients recovering from sarcopenia at six months				
Characteristics	No longer sarcopenic (n = 5)	Still sarcopenic (n = 9)	p value	n missing value
	Mean ± SD			
mMRC dyspnea scale*	-0.8	-1.0	0.79	0
Distance walked in six min (m)	+164	+81	0.24	5
Haemoglobin (g/dL)	+0.7	+0.1	0.24	4
FVC (L)	-0.31	+0.02	0.30	3
FEV1 (L)	-0.32	-0.01	0.12	3
MIP (cm H2O)	-2.0	+6.1	0.41	6
Maximal expiratory pressure (cm H2O)	+16.2	-10.9	0.09	6
Sniff nasal inspiratory pressure (cm H2O)	-4.3	-2.9	0.18	6
BODE index€	-1.5	-1.8	0.91	7
EFI scale£	+2.8	+1.6	0.49	1
Weight (kg)	+3.8	+0.5	0.10	0
Serum albumin (g/L)	+4.6	+6.1	0.44	4
Mid-arm muscle area (cm^2)	+2.3	+0.80	0.74	0
FFMI (kg/m^2)	+0.80	+0.58	0.77	0
Body fat mass index (kg/m^2)	+0.50	-0.80	0.21	0
Phase angle (degrees)	-0.84	-0.29	0.43	0

* Scores on the modified Medical Research Council (mMRC) dyspnea scale can range from 0 to 4, with a score of 4 indicating that the patient is too breathless to leave the house or becomes breathless when dressing or undressing.

€ Higher scores on the BMI, degree of airflow obstruction, dyspnea, and exercise capacity (BODE) index indicate a greater risk of death (Celli, 2004)

£ Evaluation of food intake (EFI), is a scale asking "Can you indicate the quantities you are currently eating, placing the cursor between 0 meaning "nothing at all" and 10 meaning "as usual"?

In univariate analysis (Table VII), SMI was associated with significantly better improvement for men (p = 0.01) and patients taking oral nutritional supplements (p = 0.05). For handgrip strength, a regular physical activity was associated with a better improvement (p = 0.05). In multivariate analysis, SMI and maximal inspiratory pressure (MIP) were linked: for one more SMI unit, MIP gains 3.36 units; 95% CI [0.27-6.44] p = 0.03).

TABLE VII. Factors associated with SMI and handgrip strength improvement in univariate analysis

Variables	SMI improvement		Handgrip strength improvement	
	Mean (%)	p value	Mean (%)	p value
Men	+0.39 (+5%)	**0.01**	+3.8 (+139%)	0.35
Women	-0.28 (-3%)		+1.0 (+9%)	
Physical activity	+0.36 (+6%)	0.34	+7.3 (+324%)	**0.05**
No physical activity	+0.07 (+0.4%)		+1.1 (+7%)	
ONS at discharge	+0.70 (+13%)	**0.05**	+5.2 (+66%)	0.58
No ONS at discharge	+0.08 (+0.7%)		+2.5 (+94%)	
ICS at discharge	+0.05 (+1%)	0.53	+1.6 (+16%)	0.45
No ICS at discharge	+0.22 (+3%)		+3.8 (+157%)	
Vitamin D at discharge	+0.38 (+6%)	0.44	+1.0 (+3%)	0.59
No vitamin D at discharge	+0.10 (+1%)		+3.1 (+109%)	
Artificial nutrition	+0.51 (+11%)	0.47	+10.0 (+111%)	0.18
No artificial nutrition	+0.12 (+1%)		+2.3 (+90%)	

Abbreviation: ONS = oral nutritional supplement; ICS = inhaled corticosteroid
Skeletal muscle mass index (SMI) is expressed in kg/m^2; handgrip strength is expressed in kg

Between the date of discharge from hospital and the follow-up consultation, 17 patients were readmitted for exacerbation in Pneumology: 12 once, four twice and one three times. Eight patients (15%, one woman) died, within a median of 115 days [82-139]. Kaplan-Meier survival curves are presented in Figure 3. The cause of death was an acute respiratory failure in seven cases, most often due to infectious disease. Differences in characteristics between deceased patients and survivors are detailed in the Table VIII.

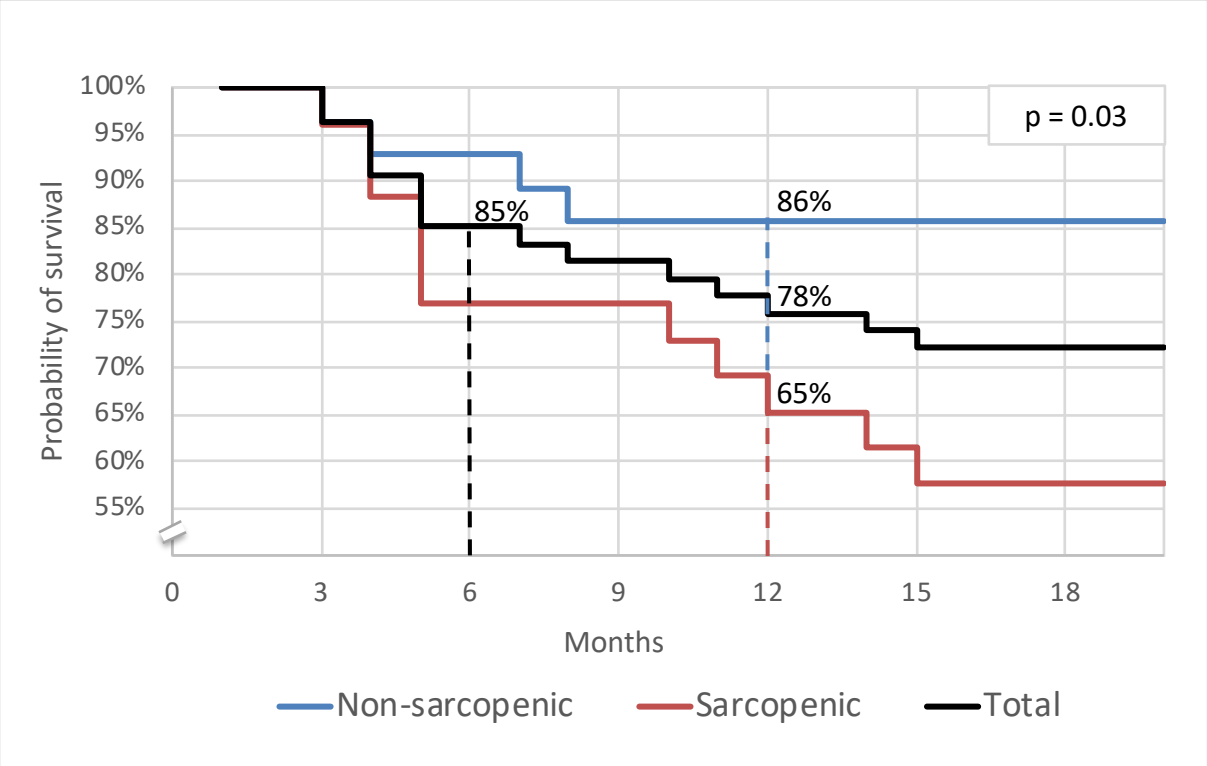

FIGURE 3. Kaplan-Meier survival curves of the first 54 patients

85% of patients survived at six months and 78% one year after the exacerbation (black curve). Sarcopenic patients (red curve) have a lower probability of survival than non-sarcopenic patients (blue curve) one year after the exacerbation (65 ± 9% vs 86 ± 7% respectively, p = 0.03).

TABLE VIII. Characteristics of the 38 patients according to whether they survived at six months				
Characteristics	Died (n = 8)	Survived (n = 30)	p value	n missing value
	Mean ± SD			
Age (year)	72 ± 10	65 ± 10	0.06	0
Men (No. and %)	7 (88%)	19 (63%)	0.39	0
Length of hospitalisation (days)	24 ± 13	14 ± 10	**0.02**	0
Number rehospitalized in six months	1.0 ± 0.9	0.2 ± 0.6	**0.006**	0
mMRC dyspnea scale*	3.5 ± 0.9	3.1 ± 1.3	0.43	0
Distance walked in six min (meters)	102 ± 37	205 ± 112	**0.05**	10
Albumin (g/L)	31.2 ± 7.3	35.4 ± 4.5	**0.05**	0
Fibrinogen (g/L)	6.0 ± 1.0	4.9 ± 1.2	**0.03**	0
CRP (mg/L)	15.4 [9.3-32.6]	13.6 [6.3-25.3]	0.92	0
FVC (L)	1.63 ± 0.63	2.52 ± 0.84	**0.02**	3
FVC (%)	60 ± 24	77 ± 18	0.06	3
FEV1 (L)	0.71 ± 0.25	1.30 ± 0.47	**0.01**	3
FEV1 (%)	37 ± 20	50 ± 15	0.07	3
MIP (cm H2O)	27 ± 13	46 ± 19	**0.01**	9
BODE index€	8.0 ± 1.2	5.6 ± 2.1	**0.02**	11
BMI (kg/m^2)	22.6 ± 9.7	28.3 ± 7.6	**0.02**	0
Handgrip strength (kg)	19.9 ± 8.0	24.6 ± 11.8	0.30	0
FFMI (kg/m^2)	15.1 ± 9.6	18.2 ± 3.9	0.06	0
SMI (kg/m^2)	7.39 ± 4.67	7.64 ± 1.71	0.07	0
Undernutrition (No. and %)	8 (100%)	24 (80%)	0.31	0
Sarcopenia (No. and %)	6 (75%)	14 (47%)	0.24	0

* Scores on the modified Medical Research Council (mMRC) dyspnea scale can range from 0 to 4, with a score of 4 indicating that the patient is too breathless to leave the house or becomes breathless when dressing or undressing.

€ Higher scores on the BMI, degree of airflow obstruction, dyspnea, and exercise capacity (BODE) index indicate a greater risk of death (Celli, 2004)

IV. Discussion

Sarcopenia was found in 48% of chronic obstructive patients during hospitalization and in 30% six months later. Skeletal muscle mass, measured by SMI, improved more in men and patients taking oral nutritional supplements and handgrip strength more in physically active patients. SMI and maximal inspiratory pressure (MIP) are linked. Sarcopenic patients had a lower probability of survival at six months than non-sarcopenic patients.

Prevalence of sarcopenia

At inclusion, the high prevalence of sarcopenia (48%) can be explained by a higher age, muscle impairment with multiple factors detailed below, and high COPD severity (47% of GOLD stage IV) which is a risk of low FFMI (48). To our knowledge, the prevalence of sarcopenia during an exacerbation had not been explored. Smoliner in Germany (49) and Rossi in Italy (50) studied geriatric hospitalized patients with a prevalence of approximately 25% of sarcopenia. In our study, nine patients were older than 80 years and seven of them were sarcopenic patients (78%) In this population, screening for sarcopenia seems essential to identify the most vulnerable subjects.

The first factor involved in muscle mass loss is anorexia, assessed by a verbal and visual scale, which was found in nearly half of the patients at the time of hospitalization. Six months later, the amelioration of dyspnea can be linked to the increase of appetite and food intake which decreases muscle wasting, inflammatory state and respiratory deficit. Physical activity could decrease anorexia too, by modulating muscle metabolism, insulin sensitivity and inflammation (51,52). The second factor, the inflammatory state, alters energy and protein requirements by elevating resting energy expenditure and nitrogen excretion. Associated with critical illness, it promotes a robust catabolism of lean body mass (53,54). Gan and co-workers were the first to note the importance of high CRP levels in COPD patients, showing that CRP is elevated in patients who actively smoked, had reduced lung

function (55) or stable COPD (56,57). This low-grade inflammation is related to the presence of airflow obstruction (58) and could be associated negatively with lung function (59,60), muscle endurance (61,62) and FFMI (63). Other factors such as recent inactivity (bed rest, deconditioning) or endocrine dysregulation (low free testosterone and vitamin D levels, higher HOMA insulin resistance) are related to loss of muscle mass. Kortebein demonstrated the effect of ten days of bed rest in healthy old individuals: study participants lost 3% of fat-free mass and 15% of muscle strength during immobilization (64).

In patients with stable chronic obstructive disease, nine of the 30 followed-patients were sarcopenic (30%), according to the EWGSOP definition. Jones showed a prevalence of 15% (65) in outpatients without unstable cardiac disease or a recent COPD exacerbation. The cutoff values of SMI used were lower (8.50 kg/m^2 for men and 5.75 kg/m^2 for women) which may explain the difference in prevalence. In a community-dwelling older people in the United Kingdom, Patel demonstrated a 6.8% prevalence of sarcopenia using the lowest third of the distribution of DEXA lean mass (66). Healthier patients may be one explanation about this low prevalence. The most recent study conducted by Byun in South Korea found 25% of sarcopenic patients (67) which is what we expected.

The evaluation of nutritional status should include a dynamic assessment of body composition changes during metabolic stress and catabolism (68). In stable patients with DEXA, we compared different muscle mass measurement techniques and found statistically high correlation with appendicular skeletal muscle index. The mid-arm muscle area, calculated from mid-arm circumference and tricipital skin fold thickness, was less precise but has the advantage to be easy, quick and inexpensive. Fat-free mass measurement (sum of water, bones, organs, excluding the fat part) using bioelectrical impedance analysis is relevant in malnutrition, sarcopenia and catabolic diseases (69,70). Because BMI is insufficient to discriminate between the different body compartments (71,72), low fat-free mass has been described in COPD and may be a better predictor of clinical outcomes in these patients. Fat-free mass is a strong predictor of peripheral muscle strength (73) and an independent predictor of survival

(74,75) but can be influenced by edema during an acute exacerbation. Compared to DEXA, the sensitivity for detecting nutritional depletion was 86% for impedancemetry and the specificity 88% (76). The reproducibility of fat-free mass measurements over a seven-week period was excellent. If DEXA is not available, impedance measurement is a reliable diagnostic tool for muscle mass loss in the absence of edema.

Sarcopenia and respiratory function

Loss of muscle mass could affect the diaphragmatic function: sarcopenic patients had lower maximal inspiratory pressure (MIP) than others. In multivariate analysis, SMI and MIP were significantly linked. Lim suggested that muscle wasting could be both a cause and a consequence of respiratory problems: lung function was positively correlated with muscle mass in the trunk or mid-thigh level, and negatively correlated with fat mass in trunk or central area (77). Muscle dysfunction may be due to inactivity induced by deconditioning (8), systemic inflammation (78), oxidative stress, blood gas disturbances, corticosteroid use and reductions in muscle mass (79). Reduced fat-free mass is associated with impaired respiratory muscle strength (80,81) in COPD, both functional muscle strength (82) and endurance (83). Collet found that the endurance of the inspiratory muscles can be altered in obese patients with a BMI greater than 40 kg/m^2 (83). Decrease in inspiratory muscle function represents an important prediction factor for the survival rate in COPD patients (85,86). The combination of endurance and strength training would be indicated for patients with significant muscle atrophy.

At six months, sarcopenic patients did not improved significantly their respiratory function other than dyspnea and distance walked in six minutes. This result can be explained by the presence of a non-reversible respiratory disorder and the persistence of smoking often not admitted in patients already having a maximum inhaled treatment. The six-minute-walk test improved of 109 ± 32 meters which is considered as clinically significant. In Redelmeier's study with stable severe COPD, the smallest difference associated with a difference in the patients' perception of exercise performance was a mean

of 54 meters (95% confidence interval, 37–71 m) (87). In contrast, Holland demonstrated a minimal difference of 25 meters (88) and Wise a statistically significant difference of 86 meters (89). Regular monitoring is needed to check long-term changes in respiratory function.

Evolution of nutritional status

We studied factors that could improve patients' nutritional status. In the 2012 Cochrane review, Ferreira reports that nutritional supplementation promotes significant weight gain (mean 1.6 kg), FFMI (mean 0.5 kg) and MIP change from baseline among patients with COPD. We found the same result of muscle mass improvement for patients with oral nutritional supplements at hospital discharge, without information about the quantity and duration of supplements taken. In Ferreira's meta-analysis of 2000, nutritional supplementation alone failed to induce significant weight gain (90) whereas in Weekes' trial, a dietary counselling and food fortification resulted in weight gain (91). We noted a better improvement of handgrip strength in patients having a regular physical activity. It has been demonstrated that physically active subjects are less likely to have low FFMI (92) and lower risk of readmission (93).

Two controlled studies have demonstrated that nutritional supplementation combined with supervised exercise training increased body weight and fat-free mass in underweight patients with COPD (81,94). A French trial undertaken in malnourished patients with chronic respiratory failure found the same result with multimodal nutritional rehabilitation combining health education, oral nutritional supplements, exercise and oral testosterone for 90 days (95). In a randomized double-blind study, 81 COPD patients with a lean mass index below the 25th percentile were enrolled in a four-months ambulatory respiratory rehabilitation program and received daily either an oral nutritional supplement or a placebo. At the end of the rehabilitation program, significant differences in favor of the supplemented group were observed in terms of weight gain, increase in respiratory muscle strength and increase in the number of daily steps evaluated by accelerometers (96).

Jones demonstrated the reversal of the sarcopenic state after a pulmonary rehabilitation (65) with 12/43 patients who were no longer considered sarcopenic at the end of the program. A respiratory rehabilitation should be offered to more patients after an acute exacerbation. Recent experimental data suggest that the endogenous peptide apelin, which is induced by muscle contraction, is positively associated with the beneficial effects of exercise in old patients (97). It could be both used as a tool for diagnosis of early sarcopenia and as the target of an innovative pharmacological strategy to prevent age-associated muscle weakness and restore physical autonomy.

Screening sarcopenia to prevent mortality

COPD is a disease with a high mortality rate. In the meta-analysis of Hoogendoorn, the mortality rate at six months of COPD exacerbation was 15.6% (98) which corresponds to our results (15%). In our study, non-survivors were older and had more airflow limitation, a shorter walking distance, higher BODE score, longer hospital stay and more rehospitalizations at six months which corresponds to Celli's results (99). The six-minute-walk test is useful to check the patient's ability to exercise and calculate the prognostic index BODE (100). In 2004, Pinto-Plata demonstrated that a shorter walked distance was associated with a higher mortality in COPD patients (25).

A second mortality factor is malnutrition (59,101) associated with impaired energy balance (102), 40% longer hospital stay (103) and 35% low lean mass (104). In a cohort of COPD patients treated with long-term oxygen therapy, a BMI under 25 kg/m^2 was a predictive factor for all-cause and respiratory mortality (105). Conversely, being overweight is only protective in patients with high muscle mass and the highest mortality is found in the low muscle mass groups (106). Advanced malnutrition syndromes are often associated with loss of muscle mass and function that will result in measurable declines in strength and physical performance. Next to weight (107,108) and CRP level (34,109,110) to predict mortality, plasma fibrinogen is a robust biomarker, significantly associated with symptoms, exercise

capacity, exacerbation rate, BODE index and mortality (111). It can be a useful biomarker to identify COPD patients with a high risk of future exacerbations and lower probability of survival (112).

Aging and chronic diseases like COPD are associated with sarcopenia (113). We found that survival was lower in sarcopenic patients, hence the importance of measuring fat-free mass and muscle strength to better predict mortality. Schols and Vestbo studied survival of COPD patients and demonstrated that fat-free mass assessed by bioelectrical impedance analysis is an independent predictor of mortality (48,114). Kilgour evaluated the association between handgrip strength and survival in advanced cancer patients and found an independent link. In the international consensus statement on sarcopenia in the elderly (16), measures of handgrip strength are recommended and patients with low handgrip strength are further tested for deficits of muscle mass. In older nursing-home residents, Landi demonstrated that sarcopenia was associated with increased risk of all-cause mortality (115). Identifying sarcopenic patients may improve survival with personalized therapeutic intervention.

Strengths and limitations of the study

The main limitation is that the fat-free mass was not measured at the same time with a reference technique, such as DEXA. Skeletal muscle mass was calculated from an bioelectrical impedance analysis equation (19) validated by Janssen (116) and Chien (117) in healthy Caucasians and Asians populations with high correlation coefficients, but not in diseased individuals. The assessment of fat-free mass may be biased during an exacerbation, partly explained by a change in the distribution of body water. At inclusion, 24% of patients had edema of the lower limbs increasing their FFMI. Therefore, the evaluation of sarcopenia should be reevaluated in a stable state, away from any exacerbation.

In addition, a quite small sample of chronic obstructive patients with different disease severity and function impairment was examined. Our study was conducted in a single center and in a cross-sectional study design, which limits the generalization of the results. Chronic obstructive patients hospitalized

in Pneumology are more severe from a respiratory but also nutritional point of view than primary care patients.

To our knowledge, this is the only study exploring the evolution of so many respiratory and nutritional parameters in chronic obstructive patients after an exacerbation. A randomized controlled trial could improve the validity of the results. We did not exclude patients who were lost to follow-up and deceased patients from the analyses so that the results could be generalized to real life COPD population seen in clinical practice.

V. Conclusion

Chronic obstructive diseases, associated with numerous comorbidities (cardio-vascular, malnutrition, skeletal muscle dysfunction, osteoporosis), require a global assessment of risks, disability and evolution. Sarcopenia, defined as skeletal muscle impairment and muscle mass loss, is an important factor to screen and to watch.

Like malnutrition, sarcopenia seems to be a poor prognostic factor. As part of a rehabilitation program, physical activity and optimal dietary intakes including protein could help reduce mortality of these patients.

At a time when the European Space Agency is interested in astronauts' nutritional diets, suffering significant muscle loss in the absence of gravity, would one day dare to imagine sending a sarcopenic COPD patient into space?

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Appendix I. Written consent

LETTRE D'INFORMATION DESTINEE AUX PATIENTS

POUR PARTICIPATION A UNE RECHERCHE BIOMEDICALE

Titre de la recherche : Prévalence de la sarcopénie chez des patients obstructifs chroniques hospitalisés en Pneumologie au CHU de Clermont-Ferrand

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Madame, Monsieur,

Vous êtes hospitalisé(e) dans le service de Pneumologie du CHU de Clermont-Ferrand (aggravation de vos symptômes respiratoires, infection pulmonaire, …).

Nous vous proposons de participer à une étude de recherche clinique, dans le cadre d'une thèse de Médecine. Cette recherche est réalisée sous la direction du Dr Annick GREIL.

Ce document vous explique le but de ce projet de recherche, ses procédures, ses avantages et inconvénients.

Avant d'accepter de participer à ce projet de recherche, veuillez prendre le temps de lire et comprendre ces informations, de réfléchir à votre participation, et de demander au médecin responsable de l'étude de vous expliquer ce que vous n'auriez pas compris. Il est important pour votre participation de lire et comprendre ce formulaire. N'hésitez pas à poser vos questions.

RESPONSABLES DE L'ETUDE

Mr Loïc PERROT, Interne de Pneumologie du CHU de Clermont-Ferrand, réalisant sa thèse de Médecine

Téléphone :

Directeur de thèse : Dr Annick GREIL, Praticien Hospitalier en Pneumologie au CHU de Clermont-Ferrand

Secrétariat de Pneumologie : 04.73.75.16.35

Coordinateur : Pr Yves BOIRIE, Chef de Service du pôle Nutrition au CHU de Clermont-Ferrand

Nutritionniste : Dr Nicolas FARIGON, Praticien Hospitalier en Nutrition au CHU de Clermont-Ferrand

Secrétariat de Nutrition : 04.73.75.49.37

Physiologiste : Pr Frédéric COSTES, Chef du Service Explorations Fonctionnelles au CHU de Clermont

Secrétariat de Physiologie : 04.73.75.16.66

BUTS DE L'ETUDE

Il s'agit d'une étude observationnelle réalisée dans le cadre d'une thèse de Médecine.

L'objectif principal est de déterminer la prévalence (proportion) de la sarcopénie (perte de la masse musculaire), via la circonférence musculaire brachiale (tour de bras) des patients hospitalisés en Pneumologie au CHU de Clermont-Ferrand.

Les autres objectifs sont :

- étudier l'évolution de paramètres nutritionnels de ces patients après hospitalisation

- identifier les déterminants de l'évolution fonctionnelle au moment de cette hospitalisation

- déterminer des phénotypes à partir de paramètres anthropométriques, fonctionnels et nutritionnels biologiques.

DEROULEMENT DE L'ETUDE

Cette étude se déroule du 1er janvier au 1er mai 2017, elle inclut tout patient hospitalisé dans le service de Pneumologie du CHU de Clermont-Ferrand ayant un trouble ventilatoire obstructif (obstruction de ses bronches), quelle qu'en soit la cause. Le nombre de patients attendu est de 50.

Chaque patient est vu en consultation par l'interne (Mr Loïc PERROT) réalisant sa thèse, d'une durée d'environ 30 minutes à 1 heure, selon les cas. Il sera proposé au patient de participer à l'étude, après information claire loyale et appropriée concernant son déroulement, les examens à réaliser et la consultation de suivi à 6 mois.

Une fois le consentement recueilli, il sera demandé au patient de remplir un ensemble de questionnaires concernant son état de santé respiratoire, son niveau d'exercice physique et son tabagisme.

Lors de cette consultation, l'interne devra réaliser un bilan nutritionnel (interrogatoire, anthropométrie, impédancemétrie, hand-grip).

Durant l'hospitalisation, il sera réalisé :

- le bilan respiratoire réalisé systématiquement en cas d'aggravation de l'état respiratoire : test de marche de 6 minutes, EFR (épreuves fonctionnelles respiratoires).

- un bilan biologique par prise de sang veineux, systématique lors de toute hospitalisation, complété par quelques paramètres biologiques sans incidence sur le volume de sang prélevé.

L'ensemble de ces examens ne modifiera ni la durée de vos traitements, ni la durée de votre hospitalisation.

Après l'hospitalisation, chaque patient sera revu systématiquement à 6 mois, en consultation pneumologique au CHU de Clermont-Ferrand, pour réaliser un bilan respiratoire et nutritionnel moins exhaustif.

A noter que vous pourrez participer simultanément à une autre recherche clinique dans le seul cas où celle-ci ne porterait pas sur la Pneumologie ou la Nutrition. Dans ce cas, merci d'en informer l'un des responsables de l'étude.

BENEFICE(S) ATTENDUS

- Accès à un bilan respiratoire et nutritionnel peu invasif lors de l'hospitalisation en Pneumologie.

- Information du patient sur son état respiratoire et nutritionnel.

- Évaluation de son risque métabolique et cardio-vasculaire, conseils vis-à-vis de ce risque.

- Suivi médical respiratoire et nutritionnel systématique à 6 mois de l'hospitalisation.

- Nous espérons améliorer la qualité des soins des personnes, qui comme vous, souffrent de troubles ventilatoires obstructifs et/ou de troubles nutritionnels. Vous aurez ainsi contribué à l'avancement des connaissances.

INCONVENIENTS ET RISQUES POTENTIELS

- Votre participation à la recherche ne devrait pas comporter d'inconvénients significatifs, si ce n'est le fait de donner de votre temps. Vous pourrez demander de prendre une pause ou de poursuivre l'entrevue à un autre moment qui vous conviendra.

- L'information sur l'état de santé de chaque patient peut générer de l'anxiété, du stress.

- La prise de sang veineux est réalisée à titre systématique pour chaque patient hospitalisé pour aggravation de ses symptômes respiratoires. Ces tests peuvent générer de l'inconfort, de l'anxiété et du stress. Le risque est une douleur post-ponction, une ecchymose ou un hématome minime. Dans ce cas, une surveillance sera réalisée durant l'hospitalisation par l'infirmière vous prenant en charge.

- Le test de marche de 6 minutes, l'EFR, l'anthropométrie, l'impédancemétrie et le hand-grip sont des examens non invasifs, ne présentant pas d'effet indésirable.

- La participation à cette étude nécessite un déplacement avec transport lors de la consultation de suivi à 6 mois.

FRAIS MEDICAUX

Votre collaboration à ce protocole de recherche biomédicale n'entraînera pas de participation financière de votre part. Conformément à la loi, tous les frais liés à l'étude seront pris en charge par le promoteur de l'étude.

LEGISLATION - CONFIDENTIALITE

Pour ce projet de recherche, le Comité de Protection des Personnes Sud-Est VI a émis un avis éthique à sa réalisation.

Toute information vous concernant recueillie pendant cet essai sera traitée de façon confidentielle.

Seuls les responsables de l'étude et éventuellement les autorités de Santé pourront avoir accès à ces données. A l'exception de ces personnes - qui traiteront les informations dans le plus strict respect du secret médical -, votre anonymat sera préservé. La publication des résultats de l'étude ne comportera aucun résultat individuel.

Les données enregistrées à l'occasion de cette étude feront l'objet d'un traitement informatisé par le promoteur. S'agissant de données nominatives, vous bénéficiez à tout moment du droit d'accès et de rectification des données vous concernant auprès des responsables de l'étude et , en ce qui concerne les informations de nature médicale, ce droit est exercé par l'intermédiaire du Docteur Annick GREIL conformément à la loi 78-17 du 06 janvier 1978 relative à l'Informatique, aux Fichiers et aux Libertés, modifiée par la loi n°94-548 du 1er juillet 1994, relative au traitement des données nominatives ayant pour fin la recherche dans le domaine de la santé. Le projet a reçu un avis favorable de la CNIL en date du 14/11/2016.

Les résultats globaux de l'étude pourront vous être communiqués si vous le souhaitez (par écrit, par téléphone ou en personne). Dans ce cas, veuillez vérifier que vos coordonnées sont à jour dans votre dossier.

Si vous avez des questions pendant votre participation à cette étude, vous pourrez contacter le médecin responsable de l'étude, le Dr Annick GREIL, tél : 04.73.75.16.35 ou l'interne réalisant sa thèse, Mr Loïc PERROT, tél :

Vous êtes libre d'accepter ou de refuser de participer à cette étude. Cela n'influencera pas la qualité des soins qui vous seront prodigués.

Vous pouvez également décider en cours d'étude d'arrêter votre participation sans avoir à vous justifier. Les renseignements recueillis seront conservés sauf opposition de votre part. Les questionnaires que vous aurez remplis ne pourront être détruits car anonymisés.

Nous vous remercions d'avoir pris le temps de lire cette lettre d'information. Si vous êtes d'accord pour participer à cette recherche, nous vous invitons à signer le formulaire de consentement ci-joint.

FORMULAIRE DE CONSENTEMENT
POUR LA PARTICIPATION A UNE RECHERCHE BIOMEDICALE

Titre de la recherche : Prévalence de la sarcopénie chez des patients obstructifs chroniques hospitalisés en Pneumologie au CHU de Clermont-Ferrand

Je soussigné(e) …… *(nom et prénom du sujet),*

Accepte de participer à l'étude « *Prévalence de la sarcopénie chez des patients obstructifs chroniques hospitalisés en Pneumologie au CHU de Clermont-Ferrand* »

Les objectifs et modalités de l'étude m'ont été clairement expliqués par l'interne Mr Loïc PERROT.

J'ai lu et compris la fiche d'information qui m'a été remise.

J'accepte que les documents de mon dossier médical qui se rapportent à l'étude puissent être accessibles aux responsables de l'étude et éventuellement aux autorités de santé. A l'exception de ces personnes, qui traiteront les informations dans le plus strict respect du secret médical, mon anonymat sera préservé.

Je pourrai exercer mon droit d'accès et de rectification auprès du Dr Annick GREIL, ou de son interne Loïc PERROT.

J'ai bien compris que ma participation à l'étude est volontaire.

Je suis libre d'accepter ou de refuser de participer, et je suis libre d'arrêter à tout moment ma participation en cours d'étude. Cela n'influencera pas la qualité des soins qui me seront prodigués.

Mon consentement ne décharge pas les organisateurs de cette étude de leurs responsabilités. Je conserve tous mes droits garantis par la loi.

Après en avoir discuté et avoir obtenu la réponse à toutes mes questions, j'accepte librement et volontairement de participer à la recherche qui m'est proposée.

Fait à CLERMONT-FERRAND,

Le ……

Nom et signature de l'investigateur *Signature du sujet*

Appendix II. Questionnaires

Scale of shortness of breath (= dyspnea) according to mMRC

Table 2.5. Modified MRC dyspnea scale[a] PLEASE TICK IN THE BOX THAT APPLIES TO YOU (ONE BOX ONLY) (Grades 0–4)	
mMRC Grade 0. I only get breathless with strenuous exercise.	❑
mMRC Grade 1. I get short of breath when hurrying on the level or walking up a slight hill.	❑
mMRC Grade 2. I walk slower than people of the same age on the level because of breathlessness, or I have to stop for breath when walking on my own pace on the level.	❑
mMRC Grade 3. I stop for breath after walking about 100 meters or after a few minutes on the level.	❑
mMRC Grade 4. I am too breathless to leave the house or I am breathless when dressing or undressing.	❑

[a] Fletcher CM. BMJ 1960; 2: 1662.

Evaluate your level of physical activity:

Please complete this questionnaire:

Concerning your level of physical activity (circle your situation):

- Never
- Regular (more than 30 minutes a day, at least three times a week)

Evaluate Your Smoking:

Please complete this questionnaire:

1. About your tobacco use (circle your situation):

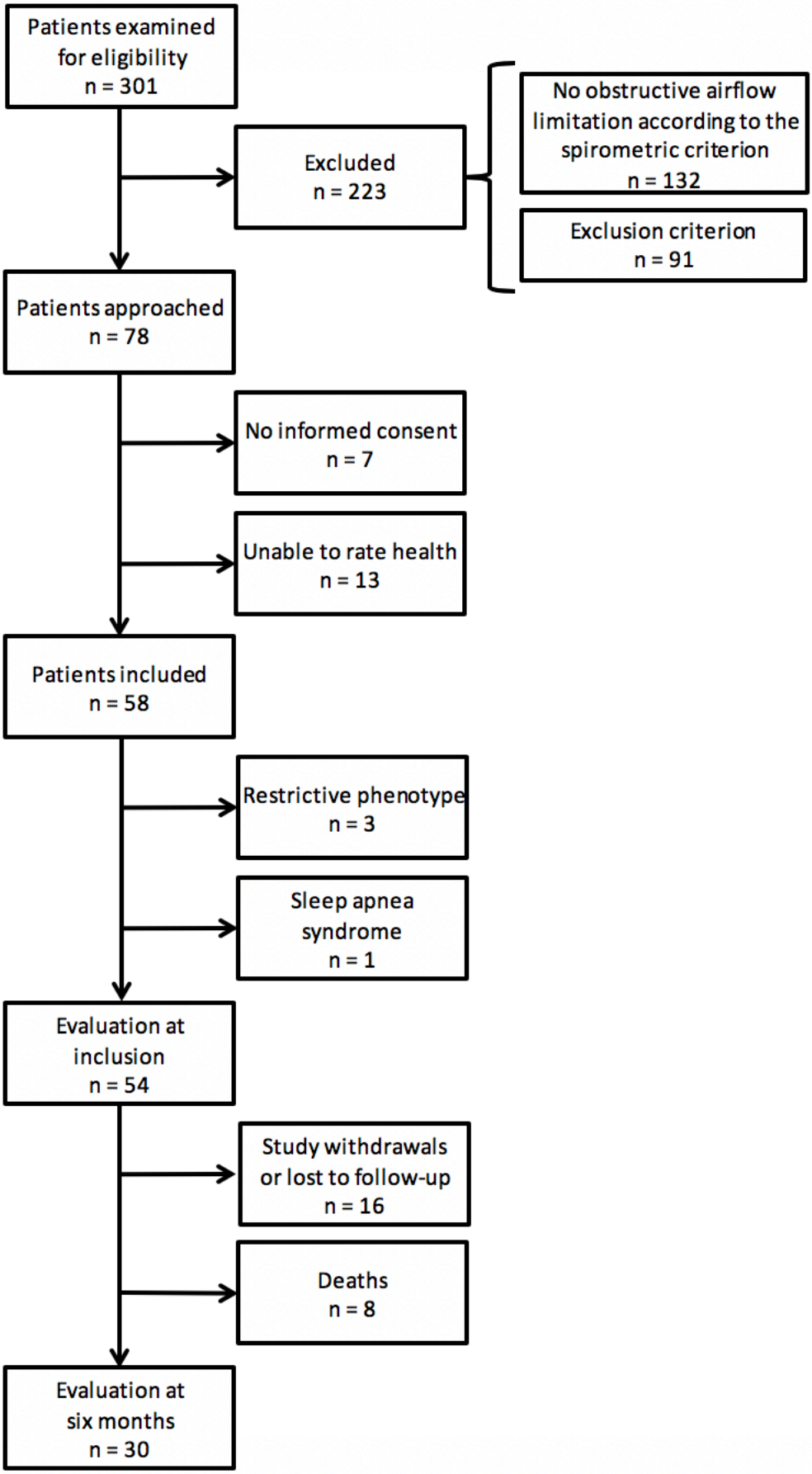
Never Stopped since ..... (month-year) Active

2. If you smoked, how many years? .....

3. If you smoked, how many cigarettes per day (average)?
.....

NB: A patient who has "never" smoked is considered to have consumed less than 100 cigarettes throughout his / her lifetime.

Appendix III. Flow chart



(Conseil national de l'ordre des médecins)

SERMENT D'HIPPOCRATE

Au moment d'être admis(e) à exercer la médecine, je promets et je jure d'être fidèle aux lois de l'honneur et de la probité.

Mon premier souci sera de rétablir, de préserver ou de promouvoir la santé dans tous ses éléments, physiques et mentaux, individuels et sociaux.

Je respecterai toutes les personnes, leur autonomie et leur volonté, sans aucune discrimination selon leur état ou leurs convictions. J'interviendrai pour les protéger si elles sont affaiblies, vulnérables ou menacées dans leur intégrité ou leur dignité. Même sous la contrainte, je ne ferai pas usage de mes connaissances contre les lois de l'humanité.

J'informerai les patients des décisions envisagées, de leurs raisons et de leurs conséquences.
Je ne tromperai jamais leur confiance et n'exploiterai pas le pouvoir hérité des circonstances pour forcer les consciences.

Je donnerai mes soins à l'indigent et à quiconque me les demandera. Je ne me laisserai pas influencer par la soif du gain ou la recherche de la gloire.

Admis(e) dans l'intimité des personnes, je tairai les secrets qui me seront confiés. Reçu(e) à l'intérieur des maisons, je respecterai les secrets des foyers et ma conduite ne servira pas à corrompre les mœurs.
Je ferai tout pour soulager les souffrances. Je ne prolongerai pas abusivement les agonies. Je ne provoquerai jamais la mort délibérément.

Je préserverai l'indépendance nécessaire à l'accomplissement de ma mission. Je n'entreprendrai rien qui dépasse mes compétences. Je les entretiendrai et les perfectionnerai pour assurer au mieux les services qui me seront demandes.

J'apporterai mon aide à mes confrères ainsi qu'à leurs familles dans l'adversité.

Que les hommes et mes confrères m'accordent leur estime si je suis fidèle à mes promesses ; que je sois déshonoré(e) et méprisé(e) si j'y manque.

SERMENT D'HIPPOCRATE

En présence des Maîtres de cette FACULTE et de mes chers CONDISCIPLES, je promets et je jure d'être fidèle aux lois de l'Honneur et de la Probité dans l'exercice de la Médecine.

Je donnerai mes soins gratuits à l'indigent et je n'exigerai jamais un salaire au-dessus de mon travail. Admis dans l'intérieur des maisons, mes yeux ne verront pas ce qui s'y passe, ma langue taira les secrets qui me seront confiés et mon état ne servira pas à corrompre les mœurs ni à favoriser le crime.

Respectueux et reconnaissant envers mes MAÎTRES, je rendrai à leurs enfants l'instruction que j'ai reçue de leurs pères.

Que les HOMMES m'accordent leur estime si je suis fidèle à mes promesses. Que je sois couvert d'OPPROBRE et méprisé de mes confrères si j'y manque.

PERROT Loïc

Prévalence de la sarcopénie chez des patients obstructifs chroniques hospitalisés en Pneumologie au CHU de Clermont-Ferrand

Thèse de Médecine, Clermont - Ferrand, 2018

RESUME :

Introduction : La BPCO s'accompagne d'une perte de masse musculaire squelettique. Associée à une diminution des performances physiques, elle définit la sarcopénie. L'objectif de cette étude est de décrire la prévalence de la sarcopénie chez des patients ayant une insuffisance respiratoire chronique obstructive pendant une hospitalisation pour exacerbation aiguë de leur maladie. L'évolution de la sarcopénie à six mois et la survie à un an de ces patients ont également été étudiées.

Méthodes *:* Nous avons inclus prospectivement des patients hospitalisés et mesuré leur composition corporelle, leur force de préhension et leur fonction respiratoire, dont la pression inspiratoire maximale (PIM) représentative de la fonction diaphragmatique. Les mêmes mesures ont été réalisées à six mois en consultation. La sarcopénie était définie par un indice de masse musculaire squelettique (IMS) bas mesuré par impédancemétrie, et une force de préhension (FP) diminuée, sur la base des critères du groupe de travail européen sur la sarcopénie chez les personnes âgées (EWGSOP). Les données de survie ont été collectées dix-huit mois après l'hospitalisation.

Résultats : Nous avons analysé les données de cinquante-quatre patients, âgés de 68 ± 9 ans et d'IMC 26,9 ± 7,8 kg/m^2, avec un VEMS moyen de 1,13 ± 0,49 L (45 ± 16 %). Une sarcopénie était observée chez 48 % des patients lors de l'hospitalisation et chez 30 % en consultation. A six mois, l'IMS s'est amélioré davantage chez les hommes que chez les femmes (+5 % vs -3 %, p = 0,01), il tend à s'améliorer plus chez les patients prenant des compléments nutritionnels oraux (+13 % vs +1 %, p = 0,05). La FP tend à augmenter plus chez les patients physiquement actifs (+324 % vs +7 %, p = 0,05). En analyse multivariée, IMS et PIM étaient liés (p = 0,03). A un an, le taux de survie était plus faible chez les patients sarcopéniques (65 % vs 86 %, p = 0,03).

Conclusion : La sarcopénie dans l'insuffisance respiratoire chronique obstructive est fréquente lors d'une exacerbation et à l'état stable. Elle expose à une survie plus faible. Une prise en charge multimodale permet de diminuer sa prévalence.

MOTS-CLES
BPCO, Composition corporelle, Évaluation nutritionnelle, Maladie pulmonaire chronique obstructive, Malnutrition, Mortalité, Prévalence, Sarcopénie

JURY

Président : Monsieur CAILLAUD Denis, Professeur, UFR de Médecine Clermont - Ferrand

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DATE DE LA SOUTENANCE
8 octobre 2018

ADRESSE DE L'AUTEUR