

Research article

The importance of Alpha-1 Antitrypsin (AAT) and respiratory rehabilitation in patients with lung diseases

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Abstract: Background: The incidence of lung diseases is very high worldwide, especially in the case of lung cancer, pulmonary tuberculosis, and obstructive ventilatory dysfunctions. Alpha-1 antitrypsin (AAT) is synthesized mainly by hepatocytes, and one of its roles is to inhibit protease activity in the body's biological fluids following the phenomenon of programmed cell death, which is also called apoptosis. Acute lung diseases, but especially chronic ones, can cause, in addition to pulmonary and extrapulmonary manifestations, social and psychological impact, which is why a complex, interdisciplinary respiratory rehabilitation program is necessary. **Objectives:** Our study aimed to determine the correlation between alpha-1 antitrypsin values and lung diseases (pulmonary tuberculosis, lung cancer, asthma, and COPD) and to evaluate the influence of the individualized respiratory rehabilitation program in these diseases. **Methods:** We carried out a retrospective study between February 2022 and March 2023 in the Pneumology Department of the "Victor Babeș" Clinical Hospital of Infectious Diseases and Pneumoftiziologie, Craiova. It included 189 patients diagnosed with pulmonary tuberculosis, lung cancer, or obstructive ventilatory dysfunctions (chronic obstructive pulmonary disease – COPD or asthma). Alpha-1 antitrypsin was collected from all patients. Respiratory rehabilitation was carried out both during hospitalization and in an out-patient setting for a maximum period of 6 months after discharge, with some patients even using telemedicine. **Results:** Increased values of alpha-1 antitrypsin were detected in advanced stages of the disease, and a clear improvement of clinical and functional parameters was observed after inclusion in the rehabilitation program. **Conclusions:** Detection of alpha-1 antitrypsin deficiency (AATD) is rare. The majority of patients diagnosed with lung cancer in advanced stages showed increased values of alpha-1 antitrypsin, AAT being able to be used as a follow-up marker in response to oncological treatment. Respiratory rehabilitation benefits in pulmonary tuberculosis, lung cancer, COPD, and asthma, regardless of the form of the disease. An interdisciplinary approach is necessary for the optimal treatment and control of lung diseases.

Keywords: respiratory rehabilitation, alfa-1 antitrypsin, lung diseases

Introduction

The incidence of lung diseases is very high worldwide, especially in the case of lung cancer, pulmonary tuberculosis and, obstructive ventilatory dysfunctions. In terms of the incidence of lung cancer, it is in second place among neoplasms and has surpassed breast cancer in women and prostate cancer in men. Known risk factors such as smoking, pollution or the predominance of the male sex no longer represent the same importance, because in recent decades we have also witnessed an increase in the number of lung cancers in non-smoking women [1]. According to the Global Tuberculosis Report 2021 published by the World Health Organization (WHO), the incidence and mortality rates associated with tuberculosis (TB) have decreased worldwide [2], but still remains the leading cause of death caused by a single infectious agent (Koch's bacillus), including among Human Immunodeficiency Virus (HIV) -positive people [3]. On the other hand, COPD and asthma are the most common progressive lung diseases, not caused by an infectious agent [4], and which represent the leading causes of mortality and morbidity worldwide [5].

Alpha-1 antitrypsin (AAT) is synthesized mainly by hepatocytes, and one of its roles is to inhibit protease activity in the body's biological fluids following the phenomenon of programmed cell death, which is also called apoptosis. As this is an acute-phase reactant, its primary role is to protect by inactivating neutrophil elastase, especially in the lung alveolar tissue, against substances synthesized during the inflammatory process. AAT plays the role of a protein that is part of the SERPIN (serine protease inhibitor supergene family). From a genetic point of view, there are several protein variants: normal variants (M alleles), deficient variants (predominantly Z and S alleles), and null variants (null alleles). Low serum AAT levels contribute to the development of COPD, by the appearance of lung emphysema lesions with onset at a young age, and the abnormal accumulation of AAT proteins increases the risk of liver disease [6]. When the concentrations of alpha 1-antitrypsin show a vital decrease - by 30-40% compared to the normal ones, the clinical manifestations begin. While children are more prone to liver diseases, adults develop lung diseases more frequently. Homozygous adult smokers with hereditary alpha-1 antitrypsin deficiency develop dyspnea or emphysema 20 years earlier than non-smokers. Liver diseases caused by hereditary deficiency of alpha-1 antitrypsin sometimes show average serum concentrations due to an acute phase reaction of the inflamed liver parenchyma. Patients with AAT deficiency (AATD) face difficulties, such as late diagnosis, underdiagnosis, and limited treatment options. To improve the evolution of the health status of patients, measures for early detection of the condition are necessary [7]. The main changes in alpha-1 antitrypsin deficiency occur in children, and they are manifested in the form of: prolonged neonatal jaundice, important liver diseases, the most serious of which is liver cirrhosis, because it is the leading cause of liver transplantation in children. In adults, AATD can be manifested by: early pulmonary emphysema, pulmonary fibrosis, rarely by unexplained bronchiectasis, nephrotic syndrome, liver cirrhosis or hepatocellular carcinoma [8]. In the situation where there is a deficiency of alpha-1 antitrypsin, pulmonary emphysema occurs as a result of a defective ratio between proteases and antiproteases with a predominant location in the lower lobes, where there is a rapid degradation of lung function, manifested by a significant reduction in FEV1 (forced expiratory volume in 1 second), as and DLCO (diffusing capacity of the lungs for carbon monoxide) [9]. If the AAT values are standard, the decline of lung function occurs as a result of the increased resistance of the airways and the loss of elastic recoil [10]. On the other hand, increased values of AAT can occur during a febrile episode, in case of inflammation or infection of the body, during pregnancy, osteoarticular diseases, autoimmune diseases, administration of oral contraceptives, or drugs containing estrogen (hormone replacement treatment).

The management of changes in AAT values, specifically AATD, involves quitting smoking, an appropriate inhaler treatment and respiratory rehabilitation [11].

Although respiratory rehabilitation was known for its benefits to medicine in the case of lung diseases, with the pandemic caused by the SARS-CoV2-2 (Severe Acute

Respiratory Syndrome Coronavirus-2) infection, it earned its place for an exceptional treatment. Acute lung diseases, but especially chronic ones, can cause, in addition to pulmonary and extrapulmonary manifestations, social and psychological impact, which is why a complex, interdisciplinary respiratory rehabilitation program is necessary. It must be adapted to the needs of each patient and depending on the complexity of the lung damage, so that the content, frequency, and duration differ [9].

Pulmonary rehabilitation has proven beneficial both in active pulmonary tuberculosis, where it has the role of determining a cure without sequelae, but especially in post-TB pulmonary sequelae that can cause radiological changes: fibrosis, bronchiectasis on scar tissue, remaining cavities, thickenings, and pleural changes, and following the performance of ventilatory functional tests - spirometry, body plethysmography, DLCO (Diffusing Capacity of the Lungs for Carbon Monoxide), anomalies may appear such as obstructive, restrictive and mixed ventilatory dysfunctions, where it has the role of increasing the effort capacity and improving the quality of life [10]. In lung cancer, the importance of pulmonary rehabilitation has been demonstrated time and time again due to decreased respiratory muscle strength – preoperatively due to tumor-generated pain and dyspnea, atelectasis, and postoperatively due to surgical trauma. Special attention is paid to psychological support, nutrition, and characteristic physical exercises [11]. Regarding obstructive ventilatory dysfunctions, the evidence base for respiratory rehabilitation is the greatest in the case of patients with COPD, unlike asthma, where it is less proven. The rehabilitation program is used to improve dyspnea, improve tolerance to effort, weakness of the respiratory muscles, but also of the limbs [12].

Aims

Our study aimed to determine the correlation between alpha-1 antitrypsin values and lung diseases (pulmonary tuberculosis, lung cancer, asthma, and COPD), and to evaluate the influence of the individualized respiratory rehabilitation program in these diseases.

2. Materials and Methods

After obtaining the approval of the Ethics Committee of our hospital, no. 137/07.12.2020 by the Declaration of Helsinki, we started the research which included 189 participants. All patients were informed about the study and signed a written consent that they agreed, both with the processing of personal data and with the necessary investigations.

Research protocol

Period and place of the research

We conducted a retrospective study between February 2022 - March 2023 in the Pulmonology Department of the Clinical Hospital of Infectious Diseases and Pneumoftziology "Victor Babeș", Craiova.

Respiratory rehabilitation was carried out both during hospitalization and in an out-patient setting for a maximum period of 6 months after discharge, with some patients even resorting to telemedicine.

AAT was processed at the Department of Laboratory Medicine within the Emergency Clinical County Hospital of Craiova.

Subjects and groups

The study included 189 patients who were divided into 3 groups: the first group (G1) included 49 patients who were diagnosed with pulmonary tuberculosis, the second group (G2) included 53 patients diagnosed with lung cancer, and the third group (G3) included 87 patients who were diagnosed with obstructive ventilatory dysfunctions. G3 was subdivided into 2 subgroups: G3a which included 45 patients diagnosed with COPD and G3b which included 42 patients diagnosed with asthma. (Table 1.).

In the context of a real need of both Romanian and international society to create an integration of patients with lung diseases and changes in alpha-1 antitrypsin in a respiratory rehabilitation program, we propose that, following our study, we will harmonize the field of research with health to achieve a proper management.

The inclusion criteria in the study were:

- Patients over 18 years old;
- Patients who collected alpha-1 antitrypsin;
- Non-pregnant women, mandatory with a negative pregnancy test;
- patients who do not take estrogen-based drugs, including oral contraceptives;
- The diagnosis of tuberculosis must be confirmed following a sputum examination or broncho-alveolar lavage with a positive culture for Mycobacterium Tuberculosis (patients with active tuberculosis at the time of inclusion in the study, without sequelae)
- The diagnosis of lung cancer must be confirmed histopathologically;
- The diagnoses of obstructive ventilatory dysfunctions must comply with the guidelines in force – COPD diagnosis according to GOLD (Global Initiative for Chronic Obstructive Lung Disease) and asthma according to GINA (Global Initiative for Asthma);
- Patients must not have severe liver damage (acute or chronic hepatitis, liver cirrhosis, hepatocellular cancer);
- Patients must not have had a myocardial infarction or stroke more recently than 6 months ago;
- Patients without severe psychiatric conditions;
- Patients who were compliant and respected the exercises included in the rehabilitation program.

Table 1. The characteristics of the patients in the studied groups.

Groups	Gender		Age				Own place	
	Male	Female	18-29 years	30-49 years	50-69 years	>70 years	Urban	Rural
G1 (49 patients)	28 (57%)	21 (43%)	13 (27%)	24 (49%)	9 (18%)	3 (6%)	18 (37%)	31 (63%)
G2 (53 patients)	29 (55%)	24 (45%)	0	9 (17%)	25 (47%)	19 (36%)	29 (55%)	24 (45%)
G3 (87 patients)	39 (45%)	48 (55%)	8 (10%)	26 (30%)	30 (34%)	23 (26%)	51 (59%)	36 (41%)
G3a (45 patients)	26 (58%)	19 (42%)	0	7 (16%)	21 (46%)	17 (38%)	28 (62%)	17 (38%)
G3b (42 patients)	13 (31%)	29 (69%)	8 (19%)	19 (46%)	9 (21%)	6 (14%)	23 (45%)	19 (55%)

Applied tests

We investigated the observation sheets of the patients and collected data from the objective examination, blood tests, sputum examination, imaging studies (Figures 1. a, 1. b, 1. c), bronchoscopy (Figures 2, 3, 4) , and histopathological examination.

The rehabilitation program included patient assessment and education, establishment of the complete diagnosis, pharmacological treatment, physical training, psychological support, and proper nutrition. Physical exercises are the basis of the medical recovery program. This program was composed of an association of two exercise modalities: continuous aerobic training and IEMT (inspiratory/expiratory muscle training). The exercise training was performed with the help of the cycle ergometer or the treadmill with a progressive increase in intensity for 30 minutes. IEMT consisted of 3 sets of 5 repetitions each, followed by breathing exercises 3 times per week alternating with exercise training. For Koch's bacillus positive patients, the rehabilitation program included posturing,

submaximal aerobic breathing exercises associated with inspiratory/expiratory respiratory muscle training with progressive intensity for 30 minutes.

All sessions included 5-min warm-up and 5-min cool down, and three series of bicep curls and chest and shoulder press with a constant load of 0.5 kg. The rehabilitation program was initiated and supervised in the hospital, for a period of 3-4 weeks, followed by an out-patient rehabilitation program, with weekly monitoring.

The benefits brought were tracked by:

- measurement of oxygen saturation of arterial blood (SaO₂) with a pulse-oximeter [13];
- evaluation of dyspnea by the Borg Scale [14];
- quantification of exercise tolerance by Six – Minute Walk Distance (6MWD) [15];
- the perception of limitation of daily activities by Patient Specific Functional Scale [16];
- healing without sequelae or with limited sequelae in the case of tuberculosis patients;
- improvement of the ECOG (Eastern Cooperative Oncology Group) Performance Status Scale in patients with lung cancer [17].

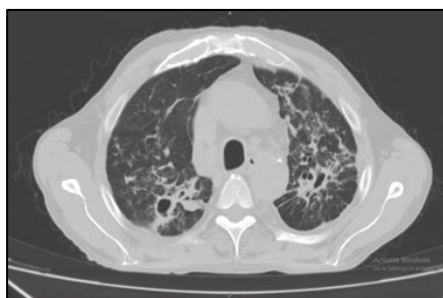


Figure 1. a.
Pulmonary tuberculosis
("tree in bud" aspects, cavity images)

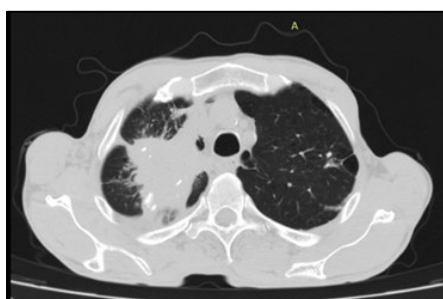


Figure 1. b.
Lung cancer
(tissue mass with dimensions of 93/59/67 mm with inhomogeneous structure and iodophilia, located in the apical and posterior segment of the right upper lobe)

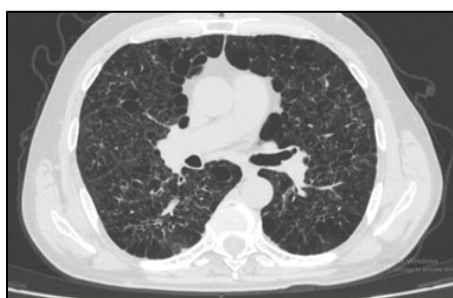


Figure 1. c.
COPD
(centrilobular and para septal emphysema located in both lung areas)

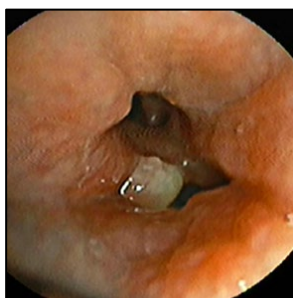


Figure 2. a.



Figure 2. b.

Figures 2. a. and 2. b. Pulmonary tuberculosis

Macroscopic appearance at bronchoscopy - middle lobe spurs with caseous necrosis.

Histopathological examination - granuloma (macrophages, multinucleated giant cells, epithelioid cells, foamy cells, these cells being surrounded by a crown of lymphocytes).

Bronchoalveolar lavage - positive BK (Koch's bacillus) direct microscopy + culture.

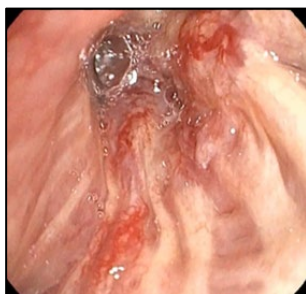


Figure 3. a.



Figure 3. b.

Figures 3. a. and 3. b. Lung cancer

Macroscopic appearance at bronchoscopy – well-vascularized infiltration of the mucosa.

Histopathological examination - squamous cell lung cancer (SQCLC).



Figure 4. a.

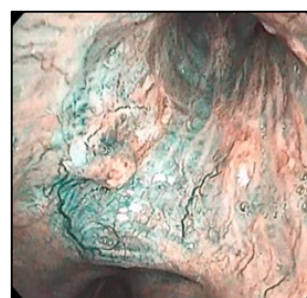


Figure 4. b.

Figures 4. a. and 4. b. COPD

Macroscopic (bronchoscopy) - diverticulosis, fibrous bands, increased sero-mucous secretions.

Histopathological examination: bronchial mucosa with subepithelial inflammatory process, with frequent foamy macrophages and siderophages.

All patients included in the study had AAT collected by the immunonephelometry method. Alpha-1 antitrypsin was collected, in the morning, from venous blood in a vacutainer without anticoagulant. The minimum required amount was 1 ml of serum. The samples were collected at the "Victor Babeș" Hospital in Craiova then, immediately after collection, they were transported under appropriate conditions (temperature 2 – 8 ° Celsius) to the Laboratory Medicine department of the Emergency Clinical County Hospital of Craiova, because the serum is separated by centrifugation on the same day.

Lipemic specimens were rejected. The reference values are 0.9 – 2.0 g/L³, with a detection limit of 0.21 g/L, and when the value is below 0.7 g/L, it indicates a high probability of homozygous deficiency.

Statistical processing

We used the Analysis ToolPak in Excel for the analytical processing of the data, and for the statistical correlation we used the Fischer test with two-tailed, which is considered to have a significant value if the p-value is below 0.005. We have highlighted the results in the form of tables and charts. The graphics were made with using the Microsoft Excel XP program.

3. Results

From the total of 189 patients included in the study, 49 were diagnosed with pulmonary tuberculosis (G1), 53 were diagnosed with lung cancer (G2), and 87 (G3) with obstructive ventilatory dysfunctions, of which 45 – 52% (G3a) were subjects with COPD, and the rest, 42 – 48% (G3b) with asthma.(Figure 5.)

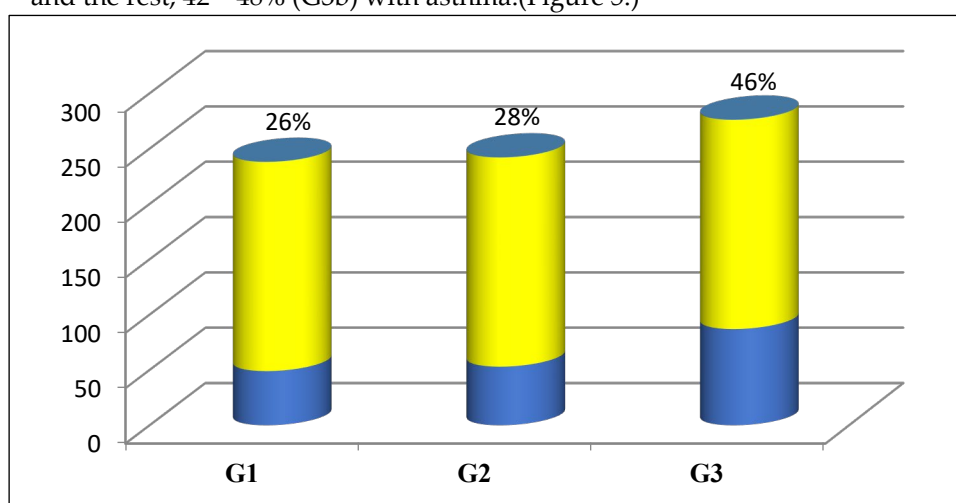


Figure 5. Distribution of patients

Among the 49 patients in group G1, 21 of them were diagnosed with minimal, unilateral lung involvement, and 28 of them with extensive forms of pulmonary tuberculosis - bilateral lung involvement. In group G2, out of the 53 patients, 17 were staged according to the Eighth Edition of TNM (Tumor, Node, Metastasis) staging in stages I-III A and 36 in stages IIIB-IV. In G3a, among the 45 patients, the patients were classified according to GOLD in the following stages: stage I (Forced Expiratory Volume FEV1 > 80%) - 7 patients, stage II (FEV1 50-79) - 21 patients, stage III (FEV1 30-49) - 11 patients and stage IV (FEV1 <30) - 6 patients. In G3b, among the 42 subjects diagnosed with asthma according to GINA, they were divided as follows: 9 subjects with mild persistent asthma, 19 subjects with moderate persistent asthma, 10 subjects with severe persistent asthma and 4 patients with very severe persistent asthma (Figure 6.).

The changes regarding AAT values consisted of increases in it. Relative to the total number of patients (189), the percentage of increase in AAT values was: for G1 – 10%, for G2 – 17% and for G3 – 8%, but relative to the total number of patients in each group, the percentages were as follows: the highest values were in group G2 – 60%, followed by group G1 – 39% and then group G3 – 18% (Figure 7.).

The increase of AAT was significantly correlated with patients with lung cancer, compared with patients diagnosed with obstructive ventilatory dysfunctions, where the two-tailed P-value equals 0.0007. This association between groups and outcomes is considered to be highly statistically significant.

We did not determine any alpha 1 antitrypsin deficiency (AATD) (Figure 8.).

In group G1, we detected 19 elevated values of AAT, of which 16 (33%) patients had bilateral pulmonary determinations, and 3 (6%) patients had limited pulmonary tuberculosis.

From the G2 group, 32 patients showed increased values of AAT, of which 27 (51%) patients were diagnosed with lung cancer divided into stages I-III A, and 5 (9%) patients into stages IIIB-IV.

The fewest patients with elevated AAT values were in the G3 group, only 16 patients out of 87, which in turn were distributed so that 9 (20%) patients belonged to the G3a group and 7 (17%) patients were included in the G3b group. Among the patients with increased values in the G3a group, 5 patients had FEV1 <30% (stage IV) and 4 patients with FEV1 30-49% (stage III). Among the patients of the G3b group, all patients with very severe persistent asthma showed increased values, i.e., 4 patients and 3 patients with severe persistent asthma.

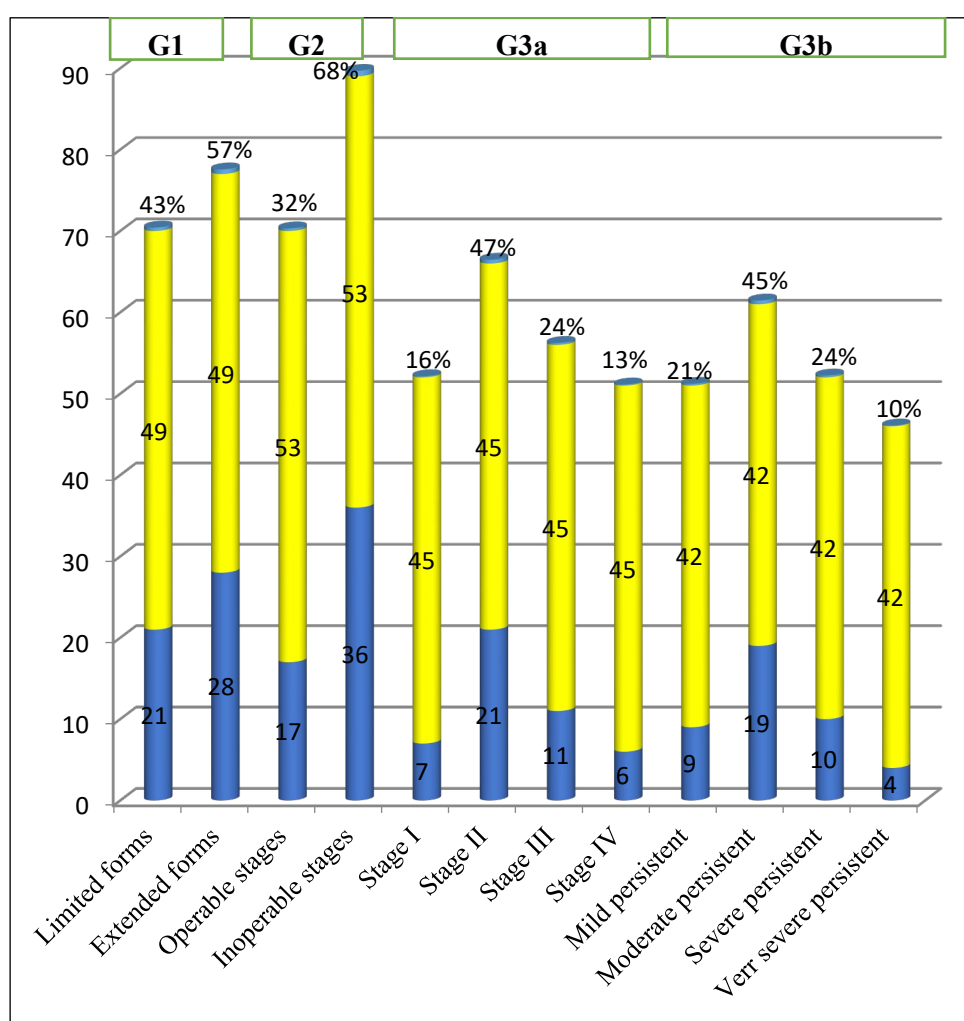


Figure 6. Staging of disease forms

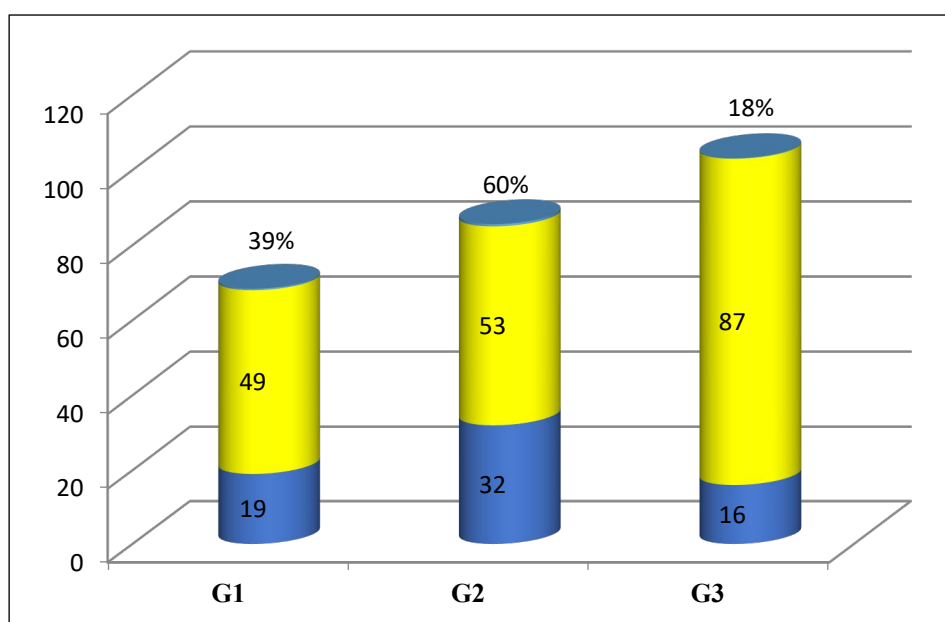


Figure 7. Correlation with increased values of AAT

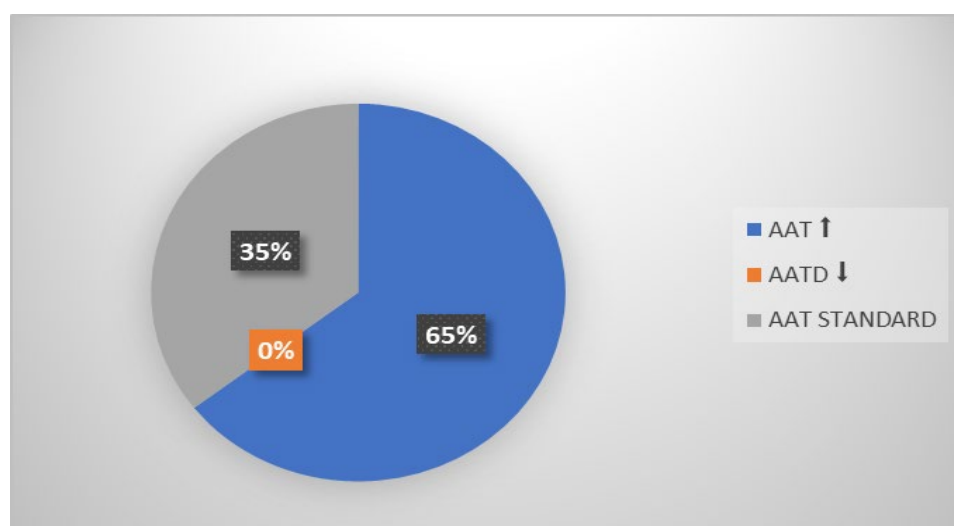


Figure 8. AAT values detected

Regarding the benefit of pulmonary rehabilitation, we found that it significantly improves the quality of life in all patients with lung diseases, with a slight difference regarding the value of AAT.

In our study, patients with elevated alpha-1 antitrypsin values showed a very little less benefit compared to patients who had normal alpha-1 antitrypsin values. This further supports the fact that patients with increased AAT values present more extensive forms of the disease.

The patients followed the rehabilitation program from the moment of hospitalization and after discharge, totaling a minimum period of 4 weeks.

The quality of life improved, dyspnea was reduced to the point of disappearance, the exercise capacity increased, and a significant improvement in oxygen saturation was observed.

Thus, in group G1 out of a total of 49 patients, 28 of the 30 patients with normal values of alpha-1 antitrypsin showed improvements after the rehabilitation program, compared to 13 of the 19 patients with increased values of AAT.

From group G2, which has a total of 53 patients, 20 of the 21 patients with normal AAT values showed benefit from respiratory rehabilitation and 26 of the 32 patients with increased values.

In group G3, which included 87 patients, improvement was detected in 10 of the 16 patients with increased AAT values and in 59 patients of the 71 with standard values. (Figure 9.)

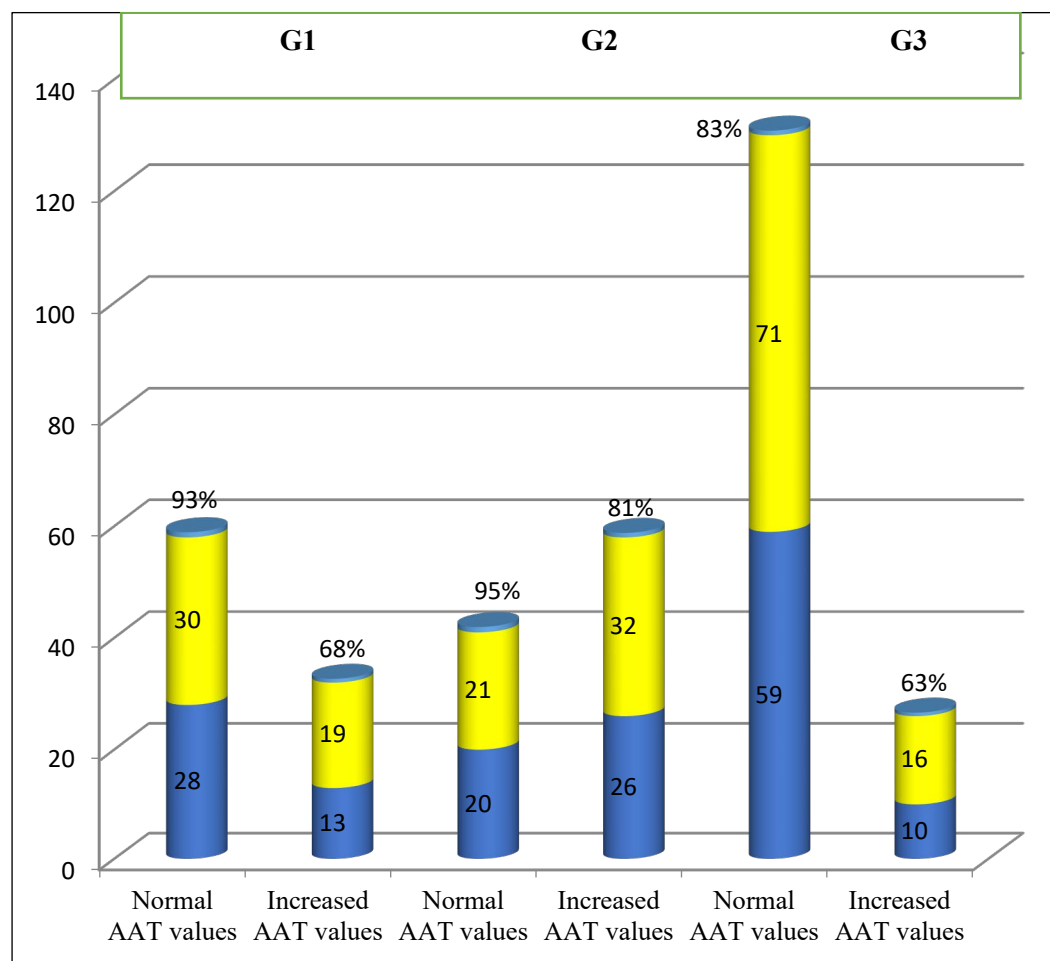


Figure 9. The benefits of respiratory rehabilitation

The complex evaluation of the results of the pulmonary rehabilitation program applied to patients with pulmonary diseases and AAT dosage represents a new field of research and little addressed until now. On the occasion of our study, we want to emphasize the importance of respiratory rehabilitation and also that it is an indispensable part of the treatment of these patients.

As can be seen in Table 2, there is a significant improvement in clinical and functional parameters after inclusion in the respiratory rehabilitation program.

Table 2. Significant improvement after respiratory rehabilitation

	SaO2		Borg Scale		6MWD		Patient-Specific Functional Scale		ECOG Performance Status Scale	
	↑ ↓		↓ ↑		↑ ↓		↑ ↓		↓ ↑	
	T1	T2	T1	T2	T1	T2	T1	T2	T1	T2
G1	23 (47%)	18 (78%)	20 (41%)	15 (75%)	25 (51%)	16 (64%)	17 (35%)	13 (76%)		
G2	29 (55%)	22 (76%)	33 (62%)	27 (82%)	36 (68%)	24 (67%)	24 (45%)	19 (79%)	31 (58%)	25 (81%)
G3a	27 (60%)	21 (78%)	31 (69%)	22 (71%)	33 (73%)	23 (70%)	21 (47%)	17 (81%)		
G3b	19 (45%)	15 (79%)	16 (38%)	11 (69%)	21 (50%)	17 (81%)	14 (33%)	11 (79%)		
P value	G1 = 0,0368* G2 = 0,0232* G3a = 0,0184* G3b = 0,0472*		G1 = 0,0958 G2 = 0,0024* G3a = 0,0754 G3b = 0,3549		G1 = 0,3270 G2 = 0,1500 G3a = 0,0853 G3b = 0,0280*		G1 = 0,0815 G2 = 0,0223* G3a = 0,0290* G3b = 0,1021		G2 = 0,0065*	
T1 (Time 1) = values before inclusion in the rehabilitation program T2 (Time 2) = values after inclusion in the rehabilitation program, minimum 3 - 4 weeks SaO2 ↓ = < 93% a.a (atmospheric air, without additional oxygen) Borg Scale ↑ = value > 5 (0 = rest, 10 = maximal effort) 6MWD ↓ = < 425 m (NYHA classes II, III, IV correspondent) Patient-Specific Functional Scale ↓ = value < 5 (0 = unable to perform an activity, 10 = able to perform an activity at the same level as before injury or problem) ECOG ↑ = > 2 (0 = fully active, 4 = completely disabled) P value* = considered statistically significant										

Thus, from group G1, 23 of the patients presented low SaO2, and after performing the exercises, 18 of the 23 subjects presented increased values of SaO2. In group G2, 29 patients had low values, and after rehabilitation, an improvement was observed in 22 of them. In G3a, 27 of the patients had low SaO2, and 21 of them showed increases in values after the program. G3b highlighted the fact that 19 of the patients had low values, and of these 15 showed an essential increase after rehabilitation. SaO2 values were between 77 %-93 % a.a. before rehabilitation and after between 93 %-100 % a.a., depending on the severity of each form.

Regarding the Borg scale before the rehabilitation program, in G1, 20 patients had scores of at least 5, with significant improvement after respiratory rehabilitation in 15 of them; in G2, 33 patients had increased values, and the benefits of rehabilitation observing in 27 of them; in G3a, 31 patients had values of at least 5, and after the program, it was observed that in 22 of them, the values decreased and in G3b 16 patients presented impressive dyspnea, but after medical rehabilitation, 11 of them had low Borg scale values.

6MWD also showed significant improvements after the rehabilitation program, so that in G1, among the 25 patients who could not complete a distance greater than 425 meters (m), after being included in the rehabilitation program, 16 of them exceeded this distance. In group G2, among the 36 patients with impaired exercise capacity, 24 of them managed to complete a distance greater than 425 m after the recovery program. In subgroup G3a it was observed that 6MWD was significantly modified in 33 patients, and after recovery it improved in 23 of them. In subgroup G3b, of the 21 patients who could not walk more than 425 m, after following the respiratory rehabilitation program 17 of them showed significant improvements.

Increases in the values of the functional scale specific to the patient were also observed after performing the respiratory rehabilitation so that in G1, 17 patients had values below 5, and 13 of them showed improvements; in G2, 24 of the subjects had low values of the scale and, 19 of them showed good values after finishing the program; in

G3a, 21 of the patients had low values and 17 of them showed significant improvements, and; in G3b of the 17 patients with values below 5, 11 of them had substantial improvements after performing correctness of the program. In G2, the improvement of the ECOG scale was also compared; of the 31 patients with a score above 2, after the end of the respiratory rehabilitation program, 25 of them had scores below 2, so with a crucial clinical improvement. The impact of the importance of rehabilitation on patients with elevated values of alpha 1 antitrypsin was also proven by the p-value.

The values were statistically significant for patients with lung cancer and COPD, which justifies the effectiveness of the rehabilitation program in these categories of respiratory patients.

4. Discussion

The originality of our study lies in the correlation of increased values of alpha-1 antitrypsin with lung diseases and the impact of pulmonary rehabilitation on these patients. The study focused on chronic lung diseases (COPD and asthma), lung cancer and active pulmonary tuberculosis with a major impact on quality of life. It is known that pulmonary rehabilitation is a basic component of the management of both chronic [18] and acute lung diseases.

We demonstrated through the Borg scale, 6MWD, patient specific functional scale, SaO₂ and the ECOG performance status scale that both patients with normal alpha -1 antitrypsin values and patients with elevated values benefited from respiratory rehabilitation.

Our study attempted to determine alpha-1 antitrypsin values in patients with lung disease, but we did not find deficient values, as opposed to standard or elevated values, in contrast to a study carried out in Spain, which claims that AATD is a widely underdiagnosed condition and which estimated that over 120,000 people in Europe have severe AATD and over 90% are undiagnosed [19]. On the other hand, an international study that included data from the European AATD Research Collaboration (EARCO) international registry that was established with the aim to characterize people with alpha-1 antitrypsin deficiency, concluded that AATD is a rare disease, but associated with a high incidence of pulmonary emphysema. [20]. In our study, the majority of patients in the G3b group had emphysema without alpha-1 antitrypsin deficiency, as a survey carried out in The Netherlands also claims that there is an underestimation of non-AATD emphysema because the mechanisms underlying the development of this are: protease-antiprotease imbalance, increased oxidative stress, programmed cell death and autophagy [21].

As we also proved, the increased levels of AAT were correlated with the most severe forms of lung disease in each category because there is the most critical inflammation. This was also supported by a study carried out in the Spanish population, which confirmed that increased levels of AAT, similar to C-reactive protein (CRP) and other markers of systemic inflammation are a vital characteristic of patients with COPD and there is a complex interrelationship between AAT values and the health of the respiratory system [22]. This fact is also supported by a study carried out in Jordan regarding neoplasias, so that increased values of AAT were associated with lung neoplasms and prostate neoplasms, significantly advanced stages, precisely as in our study, which demonstrates that plasma levels increased by AAT could be a marker for monitoring the response to cancer treatment [23].

At the same time, in this study, we proved the importance of respiratory rehabilitation in lung diseases. The importance of pulmonary rehabilitation in chronic lung diseases, such as COPD or asthma, is very well studied, and we also demonstrated in our study that it also benefits this category of patients. This is supported by a recent survey conducted in 2023 in China, which confirms that respiratory rehabilitation in COPD slows the decline of lung function, increases muscle strength, and ensures optimal neurological control and an adequate heart rate, and in asthma, exercise agents have an effect that, through a specific mechanism, causes the reduction of airway inflammation, increasing bronchial permeability and in the case of patients with eosinophilia, reducing

the number of eosinophils, which in turn reduces inflammation and implicitly the increased consumption of glucocorticoids [24]. In our study, after discharge, several patients also resorted to telrehabilitation, there being no difference between those who showed up physically and those who performed the exercises virtually, a fact also supported by a study conducted in Denmark on patients with COPD that proved that pulmonary tele-rehabilitation was not superior to classical pulmonary rehabilitation and no differences were found between groups [25].

Including patients with lung cancer, we proved the benefits of respiratory rehabilitation in this study, regardless of the stage according to TNM; this is also supported by a meta-analysis carried out in the United States of America (USA) in patients with lung cancer preoperatively which demonstrated that the exercises performed have reduced hospitalization time, prevented complications, and considerably improved exercise capacity measured by the 6-minute walk distance [26]. This was also supported postoperatively by a study conducted on 66 patients with lung cancer, in Turkey, which demonstrated that the rehabilitation program after surgery improved the quality of life, psychological manifestations and reduced dyspnea [27]. In our study, we demonstrated benefits including in the advanced stages of lung cancer, which requires palliative care by increasing the quality of life and relieving pain, and this is also supported by a study conducted in Canada on a group of patients who received an individualized respiratory rehabilitation program for 12 weeks which concluded that fatigue, depression and pain were significantly reduced and quality of life increased [28]. As Bade BC [29] and the rest of the authors said, lung cancer benefits from respiratory rehabilitation as an integral part of the treatment more than any other type of cancer due to the overlap with chronic lung diseases, especially COPD, as we also proved the satisfactory results after inclusion in the respiratory rehabilitation program.

Although the American/European Thoracic Society (ATS/ERS) pulmonary rehabilitation guidelines focus specifically on the benefit to patients with COPD, recent evidence in a literature review article indicates that rehabilitation plays an essential role in tuberculosis pulmonary, both in the active stage to ameliorate the quality of life, restore exercise capacity, prevent malnutrition and disappear dyspnea, as well as in the post-TB sequelae, which can generate obstructive, restrictive and mixed [30].

There were also limitations of the study, they consisted in the presence of comorbidities that influenced AAT values, non-compliant patients who refused to be included in the rehabilitation program or gave up along the way, and an important limitation would be the fact that we did not have the patient's genomic profile regarding the mutation of the Z gene.

For the future, we would like to integrate the alpha-1 antitrypsin dosage in the case of patients diagnosed with lung diseases, because not only AATD is important, including increased values indicate more severe forms of the disease. At the same time, we want to help implement the interdisciplinary approach to patients with lung diseases, under the conditions of application information in the three dimensions (organism, individual, society) and to offer the possibility of connection to European research topics, with the integration of the zonal specificity of situations related to functioning and disability, and their restrictions, in the concerted effort to develop optimal strategies necessary for an active life.

Our proposal solutions on life guidelines and integrated care for patients with lung diseases it represents a relevant contribution to the further development of life and working conditions for people with chronic respiratory diseases. Comparison of results our clinical trial with the results of international clinical trials will allow reporting management involving the respiratory rehabilitation of patients with lung diseases from Romania at the European and international level.

5. Conclusions

1. Detection of alpha-1 antitrypsin deficiency (AATD) is rare.
2. Elevated levels of alpha-1 antitrypsin are correlated with severe forms of lung disease due to increased inflammation.
3. The majority of patients diagnosed with lung cancer in advanced stages showed increased values of alpha-1 antitrypsin, AAT being able to be used as a follow-up marker in response to oncological treatment.
4. Respiratory rehabilitation brings benefits in pulmonary tuberculosis, lung cancer, COPD and asthma, regardless of the form of the disease.
5. An interdisciplinary approach is necessary for the optimal treatment and control of lung diseases.

6. Patents

All authors have read and agreed to the published version of the manuscript.

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study. Written informed consent has been obtained from the patients to publish this paper.

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References

1. Mederos N, Friedlaender A, Peters S, Addeo A. Gender-specific aspects of epidemiology, molecular genetics and outcome: lung cancer. *ESMO Open*. 2020; Nov;5(Suppl 4):e000796. doi: 10.1136/esmoopen-2020-000796.
2. Lin EC, Tu HP, Hong CH. Limited effect of reducing pulmonary tuberculosis incidence amid mandatory facial masking for COVID-19. *Respir Res*. 2023; Feb 17;24(1):54. doi: 10.1186/s12931-023-02365-x.
3. MacNeil A, Glaziou P, Sismanidis C, Date A, Maloney S, Floyd K. Global Epidemiology of Tuberculosis and Progress Toward Meeting Global Targets - Worldwide, 2018. *MMWR Morb Mortal Wkly Rep*. 2020; Mar 20;69(11):281-285. doi: 10.15585/mmwr.mm6911a2.
4. Holtjer JCS, Bloemsma LD, Beijers RJHCG, Cornelissen MEB, Hilvering B, Houweling L, Vermeulen RCH, Downward GS, Maitland-Van der Zee AH. Identifying risk factors for COPD and adult-onset asthma: an umbrella review. *Eur Respir Rev*. 2023; May 3;32(168):230009. doi: 10.1183/16000617.0009-2023.
5. Dasgupta S, Ghosh N, Bhattacharyya P, Roy Chowdhury S, Chaudhury K. Metabolomics of asthma, COPD, and asthma-COPD overlap: an overview. *Crit Rev Clin Lab Sci*. 2023; Mar;60(2):153-170. doi: 10.1080/10408363.2022.2140329. Epub 2022 Nov 24.
6. Janciauskiene SM, Bals R, Koczulla R, Vogelmeier C, Köhnlein T, Welte T. The discovery of α 1-antitrypsin and its role in health and disease. *Respir Med*. 2011; Aug;105(8):1129-39. doi: 10.1016/j.rmed.2011.02.002. Epub 2011 Mar 1.
7. Dasí F. Alpha-1 antitrypsin deficiency. *Med Clin (Barc)*. 2023; Nov 21:S0025-7753(23)00648-6. English, Spanish. doi: 10.1016/j.medcli.2023.10.014. Epub ahead of print.
8. Stoller JK, Hupertz V, Aboussouan LS. Alpha-1 Antitrypsin Deficiency. 2006; Oct 27 [Updated 2023 Jun 1]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK1519/>.

9. Toumpanakis D, Usmani OS. Small airways disease in patients with alpha-1 antitrypsin deficiency. *Respir Med.* 2023 May;211:107222. doi: 10.1016/j.rmed.2023.107222. Epub 2023 Mar 23.
10. Timmins SC, Diba C, Farrow CE, Schoeffel RE, Berend N, Salome CM, King GG. The relationship between air-flow obstruction, emphysema extent, and small airways function in COPD. *Chest.* 2012 Aug;142(2):312-319. doi: 10.1378/chest.11-2169.
11. Jesper Dichmann de Vos JD, Hillberg O, Perch M, Jensen JU, Wilcke JT, Løkke A. [Alpha-1-antitrypsin deficiency]. *Ugeskr Laeger.* 2021 Jul 26;183(30):V02210150. Danish.
12. Spruit MA, Wouters EFM. Organizational aspects of pulmonary rehabilitation in chronic respiratory diseases. *Respirology.* 2019; Sep;24(9):838-843. doi: 10.1111/resp.13512. Epub 2019 Feb 27.
13. Migliori GB, Caminero Luna J, Kurhasani X, van den Boom M, Visca D, D'Ambrosio L, Centis R, Tiberi S. History of prevention, diagnosis, treatment and rehabilitation of pulmonary sequelae of tuberculosis. *Presse Med.* 2022; Sep;51(3):104112. doi: 10.1016/j.lpm.2022.104112. Epub 2022 Feb 4.
14. Zhao C, Bi Y. Effect of lung rehabilitation exercise on the postoperative respiratory function of patients with lung cancer. *Asian J Surg.* 2022; Oct;45(10):2012. doi: 10.1016/j.asjsur.2022.04.062. Epub 2022 Apr 28.
15. Osadnik CR, Singh S. Pulmonary rehabilitation for obstructive lung disease. *Respirology.* 2019; Sep;24(9):871-878. doi: 10.1111/resp.13569. Epub 2019 Apr 30.
16. Singhal A, Prafull K, Daulatabad VS, John NA, John J. Arterial Oxygen Saturation: A Vital Sign? . *Niger J Clin Pract.* 2023; Nov 1;26(11):1591-1594. doi: 10.4103/njcp.njcp_2026_21. Epub 2023 Dec 4.
17. Shariat A, Cleland JA, Danaee M, Alizadeh R, Sangelaji B, Kargarfard M, Ansari NN, Sepehr FH, Tamrin SBM. Borg CR-10 scale as a new approach to monitoring office exercise training. *Work.* 2018; 60(4):549-554. doi: 10.3233/WOR-182762.
18. Enright PL. The six-minute walk test. *Respir Care.* 2003; Aug;48(8):783-5.
19. Nicholas P, Hefford C, Tumilty S. The use of the Patient-Specific Functional Scale to measure rehabilitative progress in a physiotherapy setting. *J Man Manip Ther.* 2012;Aug;20(3):147-52. doi: 10.1179/2042618612Y.0000000006.
20. Simcock R, Wright J. Beyond Performance Status. *Clin Oncol (R Coll Radiol).* 2020; Sep;32(9):553-561. doi: 10.1016/j.clon.2020.06.016. Epub 2020 Jul 16.
21. Spruit MA, Singh SJ, Garvey C, ZuWallack R, Nici L, Rochester C, Hill K, Holland AE, Lareau SC, Man WD, Pitta F, Sewell L, Raskin J, Bourbeau J, Crouch R, Franssen FM, Casaburi R, Vercoulen JH, Vogiatzis I, Gosselink R, Clini EM, Effing TW et al. ATS/ERS Task Force on Pulmonary Rehabilitation. An official American Thoracic Society/European Respiratory Society statement: key concepts and advances in pulmonary rehabilitation. *Am J Respir Crit Care Med.* 2013; Oct 15;188(8):e13-64. doi: 10.1164/rccm.201309-1634ST. Erratum in: *Am J Respir Crit Care Med.* 2014 Jun 15;189(12):1570.
22. Torres-Durán M, Lopez-Campos JL, Barrecheguren M, Miravittles M, Martinez-Delgado B, Castillo S, Escribano A, Balloira A, Navarro-Garcia MM, Pellicer D, Bañuls L, Magallón M, Casas F, Dasí F. Alpha-1 antitrypsin deficiency: outstanding questions and future directions. *Orphanet J Rare Dis.* 2018; Jul 11;13(1):114. doi: 10.1186/s13023-018-0856-9.
23. Miravittles M, Turner AM, Torres-Duran M, Tanash H, Rodríguez-García C, López-Campos JL, Chlumsky J, Guimaraes C, Rodríguez-Hermosa JL, Corsico A, Martinez-González C, Hernández-Pérez JM, Bustamante A, Parr DG, Casas-Maldonado F, Hecimovic A, Janssens W. Clinical and functional characteristics of individuals with alpha-1 antitrypsin deficiency: EARCO international registry. *Respir Res.* 2022; Dec 16;23(1):352. doi: 10.1186/s12931-022-02275-4. Erratum in: *Respir Res.* 2023 Feb 18;24(1):57.
24. Janssen R, Piscaer I, Franssen FME, Wouters EFM. Emphysema: looking beyond alpha-1 antitrypsin deficiency. *Expert Rev Respir Med.* 2019;Apr;13(4):381-397. doi: 10.1080/17476348.2019.1580575. Epub 2019 Feb 22.

25. Janciauskiene S, DeLuca DS, Barrecheguren M, Welte T, Miravittles M, Committee, Scientific and coordinators, Participating sites and. Serum Levels of Alpha1-antitrypsin and Their Relationship With COPD in the General Spanish Population. *Arch Bronconeumol (Engl Ed)*. 2020; Feb;56(2):76-83. English, Spanish. doi: 10.1016/j.arbres.2019.03.001. Epub 2019 May 30.
26. El-Akawi ZJ, Al-Hindawi FK, Bashir NA. Alpha-1 antitrypsin (alpha1-AT) plasma levels in lung, prostate and breast cancer patients. *Neuro Endocrinol Lett*. 2008; Aug;29(4):482-4.
27. Xiong T, Bai X, Wei X, Wang L, Li F, Shi H, Shi Y. Exercise Rehabilitation and Chronic Respiratory Diseases: Effects, Mechanisms, and Therapeutic Benefits. *Int J Chron Obstruct Pulmon Dis*. 2023; Jun 19;18:1251-1266. doi: 10.2147/COPD.S408325.
28. Hansen H, Bieler T, Beyer N, Kallemose T, Wilcke JT, Østergaard LM, Frost Andeassen H, Martinez G, Lavesen M, Frølich A, Godtfredsen NS. Supervised pulmonary tele-rehabilitation versus pulmonary rehabilitation in severe COPD: a randomised multicentre trial. *Thorax*. 2020; May;75(5):413-421. doi: 10.1136/thoraxjnl-2019-214246. Epub 2020 Mar 30.
29. Pu CY, Batarseh H, Zafron ML, Mador MJ, Yendamuri S, Ray AD. Effects of Preoperative Breathing Exercise on Postoperative Outcomes for Patients With Lung Cancer Undergoing Curative Intent Lung Resection: A Meta-analysis. *Arch Phys Med Rehabil*. 2021; Dec;102(12):2416-2427.e4. doi: 10.1016/j.apmr.2021.03.028. Epub 2021 Apr 27.
30. Şahin H, Naz İ, Aksel N, Güldaval F, Gayaf M, Yazgan S, Ceylan KC. Outcomes of pulmonary rehabilitation after lung resection in patients with lung cancer. *Türk Gogus Kalp Damar Cerrahisi Derg*. 2022; Apr 27;30(2):227-234. doi: 10.5606/tgkdc.dergisi.2022.21595
31. Ester M, Culos-Reed SN, Abdul-Razzak A, Daun JT, Duchek D, Francis G, Bebb G, Black J, Arlain A, Gillis C, Galloway L, Capozzi LC. Feasibility of a multimodal exercise, nutrition, and palliative care intervention in advanced lung cancer. *BMC Cancer*. 2021; Feb 13;21(1):159. doi: 10.1186/s12885-021-07872-y
32. Bade BC, Thomas DD, Scott JB, Silvestri GA. Increasing physical activity and exercise in lung cancer: reviewing safety, benefits, and application. *J Thorac Oncol*. 2015; Jun;10(6):861-71. doi: 10.1097/JTO.0000000000000536. Erratum in: *J Thorac Oncol*. 2015 Dec;10(12):1712.
33. Akkerman OW, Ter Beek L, Centis R, Maeurer M, Visca D, Muñoz-Torrico M, Tiberi S, Migliori GB. Rehabilitation, optimized nutritional care, and boosting host internal milieu to improve long-term treatment outcomes in tuberculosis patients. *Int J Infect Dis*. 2020; Mar;92S:S10-S14. doi: 10.1016/j.ijid.2020.01.029. Epub 2020 Jan 23.