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Evaluation of the functional profile of bronchopulmonary cancer patients based on biomarkers in relation to the International Classification of Functioning, Disability and Health

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Abstract

Patients with lung cancer commonly report a broad spectrum of symptoms driven by both side effects of treatment and aggressive progression of disease. As a result, growing evidence indicates that pulmonary rehabilitation (PR) can meaningfully improve exercise performance, health-related quality of life (QoL), fatigue, and dyspnea. The core objective of any PR program is to improve the patient's overall functional profile. In this study conducted at the Marius Nasta Institute of Pneumophthisiology, Bucharest, Romania, we assessed the functional profile of patients with non-small cell lung cancer (NSCLC) – specifically lung adenocarcinoma (LUAD) and squamous cell carcinoma (SCC) – and explored its relationship with key biomarkers: programmed death-ligand 1 (PD-L1), anaplastic lymphoma kinase (ALK), and epidermal growth factor receptor (EGFR). Functional status was evaluated using the International Classification of Functioning, Disability, and Health–Rehabilitation Core Set (ICF–RCS). Exercise capacity was measured with the 6-Minute Walk Distance (6MWD) test, health-related QoL was evaluated using the validated *European Organization for the Research and Treatment of Cancer* Core Quality of Life 30-item Questionnaire (EORTC QLQ-C30) questionnaire and anxiety levels were assessed with the Generalized Anxiety Disorder 7-item (GAD-7) instrument. The study identified a correlation between the patients' functional profiles and specific biomarker patterns. Based on these findings, we believe that incorporating biomarker information into functional evaluation could help build a clearer and more clinically relevant understanding of patient needs during PR, ultimately contributing to more personalized comprehensive care. We propose that future research should examine whether the relationship between biomarker status and functional, psychological, and QoL outcomes remains consistent following a structured rehabilitation program, and whether these biological markers can predict which patients are most likely to experience functional and emotional improvements. Such insight could prove valuable in guiding individualized rehabilitation strategies for patients with NSCLC.

Keywords: biomarkers, non-small cell lung cancer, pulmonary rehabilitation.

Introduction

Ahead of World Cancer Day, the *World Health Organization* (WHO), in collaboration with the *International Agency for Research on Cancer* (IARC), released updated estimates describing the global cancer burden. Using the most reliable data available, *IARC* reported that 2022 accounted for approximately 20 million new cancer diagnoses and 9.7 million cancer-related deaths. Among all malignancies, bronchopulmonary cancer ranked first worldwide, with about 2.5 million (12.4%) new cases, and remained the leading cause of cancer mortality, responsible for 1.8 million deaths (8.7% of all cancer deaths) [1].

Lung adenocarcinoma (LUAD) makes up more than 50% of all lung cancer cases. Advancements in diagnosis and treatment have enhanced both the overall survival rates and health-related quality of life (QoL) for LUAD patients. Nevertheless, the five-year survival rate for those with metastatic LUAD is less than 20% [2]. Moreover, both the incidence and mortality rates for lung cancer have increased over recent years [3]. They primarily develop in the peripheral regions and are histologically defined by the presence of glandular differentiation and/or mucin production [4, 5].

Squamous cell carcinoma (SCC) of the lung is the second most common form of non-small cell lung cancer (NSCLC), following adenocarcinoma [6]. In many cases, it is classified as a central lung tumor; nevertheless, a meaningful proportion is found in the peripheral regions [7]. The characteristic morphological features of squamous

transformation include intercellular bridges, individual cell keratinization, and squamous pearl formation [8].

It is widely accepted that lung cancer develops from a multifactorial interplay of various morphological, molecular, and genetic changes, ultimately leading to a malignant cell mass that shows the hallmark phenotypic features of cancer [9]. The accumulation of multiple molecular alterations leads to an imbalance between tumor suppressor genes (TSGs) and oncogenes that promote tumor growth, granting a cell the potential to become malignant [10]. Notably, the acquisition of somatic mutations in key oncogenes has emerged as significant "driver" events in the development of lung cancer, prompting the concept of "oncogene addiction" [11, 12]. The identification and characterization of these "driver" events have facilitated the development of targeted therapies specific to particular lung cancer subtypes.

Recent advances in therapy have highlighted the importance of a multidisciplinary model of care for lung cancer. Data indicate that high-volume centers with multidisciplinary teams treat lung cancer patients more efficiently than low-volume or non-multidisciplinary centers, which leads to more comprehensive staging, better adherence to guidelines, and improved survival rates. It is critical to reach an accurate and detailed morphological and biological definition, which frequently requires the collection of provocative tissue samples. Most therapeutic decisions are guided by the information obtained from the specimen during the diagnostic process.

The histological assessment of NSCLC is an important component in guiding treatment options and needs to be as precise and comprehensive as the available specimens and technology permit. Given that most NSCLC patients are diagnosed with advanced, unresectable conditions, it is essential that all diagnoses influencing treatment decisions are derived from small biopsy or cytological samples [13].

Epidermal growth factor receptor (EGFR) is a receptor tyrosine kinase (RTK) in many cases present on the surface of epithelial cells and is frequently overexpressed in several types of human cancers. The most frequently observed mutations in *EGFR*, such as exon 19 deletions and the *p.L858R* point mutation in exon 21, are linked to sensitivity to oral EGFR tyrosine kinase inhibitor (TKI) treatment.

Anaplastic lymphoma kinase (ALK) is a RTK that may undergo rearrangement in NSCLC, leading to dysregulated signaling through the ALK kinase domain. The presence of an ALK rearrangement correlates with responsiveness to oral ALK TKIs.

Programmed death-ligand 1 (PD-L1) is a co-regulatory molecule that can be found on tumor cells, where it hinders T-cell-mediated apoptosis. T-cells have programmed death-1 (PD-1), a negative regulator that interacts with ligands like PD-L1 [cluster of differentiation (CD)274] or PD-L2 (CD273). When PD-L1 is present, T-cell function is inhibited. Checkpoint inhibitor antibodies disrupt the interaction between PD-1 and PD-L1, enhancing the antitumor activity of the body's own T-cells [14].

The International Classification of Functioning, Disability, and Health (ICF) is a framework created by the *WHO* to evaluate individual functioning, disability, and health. Rather than categorizing individuals, the ICF describes a person's situation across various health-related domains. Its fundamental concept is that health and illness emerge from the dynamic interplay between an individual's health status (including body structures and functions, activities, and participation), personal factors (such as age, gender, race, and other health conditions), and environmental factors (like access to healthcare and social support). This framework is known as the biopsychosocial model of human functioning within the environment. To make the ICF easier to use in daily practice, the *WHO* and the ICF Research Branch developed a method for creating "ICF Core Sets" – selected groups of important ICF categories. These "Core Sets" help describe a person's functioning more clearly, especially in clinical settings, by providing focused lists of categories related to specific health conditions and care situations [15]. In this study, the ICF–Rehabilitation Core Set (ICF–RCS) was used.

Pulmonary rehabilitation (PR) is a widely adopted practice that has for many years been a vital component of comprehensive care for patients with chronic lung diseases. It is highly recommended across global clinical care standards. Substantial evidence supports this approach, demonstrating that PR leads to significant enhancements in exercise capacity, symptom relief, and overall health-related QoL, while also reducing hospitalizations and potentially improving survival rates. The primary goal of rehabilitation has always been to improve health-related QoL for individuals living with medical conditions, whether they are acute, chronic, or progressively debilitating. Patients with bronchopulmonary cancer experience a range of symptoms, driven by both the side effects of treatment and the rapid progression of the disease. Common symptoms in these patients include muscle weakness and significant weight loss, which can progress to cachexia [16]. Increasing evidence suggests that PR can significantly improve various important aspects for lung cancer patients, including exercise performance, health-related QoL, fatigue levels, and dyspnea [17]. This improvement is widely recognized in the medical community, with the agreement that rehabilitation is essential at all stages of the disease [18]. Nevertheless, the specific role of PR in the clinical management of lung cancer patients remains somewhat unclear. Additionally, there is currently no standardization of program components, and data regarding PR programs designed for lung cancer patients is limited.

Aim

The aim of our study was to assess the functional status of patients with NSCLC at the outset of the rehabilitation program, establishing a correlation between histopathological types and biomarkers, all in accordance with the ICF-RCS classification system proposed by the *WHO*. Additionally, exercise tolerance was assessed through the 6-Minute Walk Distance (6MWD), while patients' health-related QoL and anxiety levels were quantified using the *European Organization for the Research and Treatment of Cancer* Core Quality of Life 30-item Questionnaire (EORTC QLQ-C30), and the Generalized Anxiety Disorder 7-item (GAD-7) scale.

Patients, Materials and Methods

Study design

This was a prospective observational study conducted at the Marius Nasta Institute of Pneumophthisiology,

Bucharest, Romania, and received approval from both the Ethics Committee of the University of Medicine and Pharmacy of Craiova, Romania (Approval No. 91/19.02. 2024) and the Ethics Committee of the above-mentioned Institute (Approval No. 23361/17.10.2023).

Patients were enrolled consecutively, as they presented to the department and met the inclusion criteria. The investigators had authorized access to the clinical and functional data collected during routine care.

The only study-related procedures consisted of obtaining written informed consent and providing standardized questionnaires (ICF–RCS, GAD-7, and EORTC QLQ-C30), as well as performing the 6MWD test, all of which are routine, non-interventional assessments. Consequently, the study remained entirely observational and non-interventional.

Sixty-two patients [*n*=44 females (F), *n*=18 males (M)] were enrolled in the study carried out at the Marius Nasta Institute of Pneumophthisiology between November 2023 and September 2024. All study participants were patients aged 18 years and older, not only with a confirmed diagnosis of LUAD or SCC, but with a complete set of immuno-histochemistry, and all were indicated for respiratory rehabilitation.

The inclusion criteria were as follows: patients with a diagnosis of bronchopulmonary cancer, patients must demonstrate compliance with treatment protocols and ethical standards in the medical field, Romanian residents who were available to respond to the questionnaire, regular consultations with a medical specialist from the rehabilitation team in a dedicated medical environment, along with ongoing communication with the physiotherapist to facilitate the effective execution of the exercise sessions.

The following exclusion criteria have been considered: unstable cardiac conditions that could distort statistical outcomes and significantly impact the patient's health status, neuromotor disabilities that might adversely affect both the patient's locomotion and the statistical results of the study, severe orthopedic or traumatic conditions that could limit participation in the rehabilitation program, thromboembolic disorders, rheumatic conditions that affect locomotion and grasping abilities, any other condition affecting various systems in the body that could have ramifications on respiratory function and the individual's exercise capacity, cognitive impairments that restrict the ability to provide written informed consent and intellectual limitations that obstruct collaboration with the therapist during rehabilitation.

To ensure transparency in the enrollment process, a Consolidated Standards of Reporting Trials (CONSORT)-style flow description was prepared. A total of 81 patients were initially evaluated for eligibility (*n*=49 F, *n*=32 M). Of these, 10 patients were excluded due to neuromotor disabilities that limited locomotion (*n*=3 F, *n*=7 M), and seven patients were excluded because of unstable cardiac conditions representing contraindications for participation (*n*=2 F, *n*=5 M). After applying these exclusions, 64 patients remained eligible (*n*=44 F, *n*=20 M). From this group, two patients later withdrew (*n*=2 M). The final study population therefore consisted of 62 patients (*n*=44 F, *n*=18 M), all of whom completed the baseline (T0) functional and psychological assessments (Figure 1).

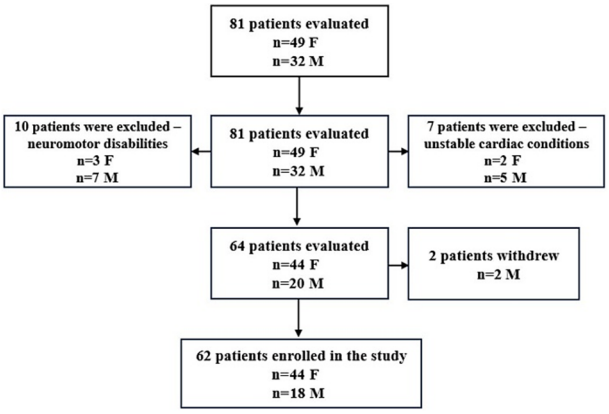

Figure 1 – ***Consolidated Standards of Reporting Trials (CONSORT) overview of patient selection. F: Females; M: Males.***

Participants completed a five-day-per-week program for eight weeks.

The rehabilitation program include: functional evaluation of each patient in order to create a personalized plan by a multidisciplinary team; physical therapy of the chest, typically performed two times a day – postural drainage and light chest percussion, active cycle of breathing techniques (combing breathing exercises with thoracic expansion exercises and forced expiratory techniques); kinesiotherapy – exercises for the respiratory muscles, exercises to educate the cough, exercises to increase exercise tolerance (aerobic training – bicycle, treadmill); psychological counselling – help, moral support; nutritional counselling – adopting a healthy lifestyle.

Instruments and measurements

Upon consent to participating in the study, exercise capacity was evaluated using the 6MWD test [19].

The patients' health-related QoL was evaluated through the validated EORTC QLQ-C30 questionnaire, specifically designed for individuals with bronchopulmonary cancer [20]. Additionally, the level of anxiety for each participant was measured using the GAD-7 questionnaire, which categorizes anxiety into four levels: 0–5 indicates no anxiety, 6–10 represents mild anxiety, 11–15 denotes moderate anxiety, and 16–21 signifies severe anxiety [21].

From the observation sheets of the patients, we extracted the personal factors: age, sex, body mass index (BMI), smoker/non-smoker, peripheral oxygen saturation (SpO_2) in the atmospheric air (Table 1).

Table 1 – ***Studied patient data***

Patients	*n*=62		
Age [years]	69.9±8.87		
Sex	44 F	18 M	
Smokers	24 Smokers	12 Non-smokers	26 Former smokers
SpO_2 [%]	94.8±3.09		
BMI [kg/m^2]	23.4±4.16		
Cancer type	29 Squamous	33 Adenocarcinoma	
PD-L1	35 Negative (≤1%)	27 Positive	
EGFR	56 Negative	6 Positive (with mutation)	
ALK	58 Negative	4 Positive	

ALK: Anaplastic lymphoma kinase; BMI: Body mass index; EGFR: Epidermal growth factor receptor; F: Females; M: Males; *n*: No. of patients; PD-L1: Programmed death-ligand 1; SpO_2: Peripheral oxygen saturation.

The functional profile of the patients was developed using the ICF–RCS framework, from which we extracted 11 codes, categorized into sections related to "Body Functions", "Activity and Participation" and "Environmental factors". ICF codes necessitate the application of one or more qualifiers to specify the extent of a problem or level of health. Analyzing these codes involved a quantitative assessment of the qualifiers, reflecting the range or magnitude of impairment in accordance with ICF methodology, as presented in Table 2.

All participants underwent flexible bronchoscopy to obtain tissue samples for histopathological assessment. Depending on the anatomical location of the lesion, either transbronchial or endobronchial biopsies were conducted. Tissue specimens were fixed in 10% neutral buffered formalin, embedded in paraffin, and sectioned at 3–5 μm thickness for microscopic examination. Initial analysis was conducted using Hematoxylin–Eosin (HE) staining to evaluate tissue architecture and cellular morphology. These aspects are illustrated in Figures 2–5.

Table 2 – ***Recommended coding practices for documenting performance and capacity in the activities and participation section of the ICF used in clinical assessments***

Qualifier	Difficulty level	Scale of the problem	
xxx.0	NO difficulty	(none, absent, negligible, …)	0–4%
xxx.1	MILD difficulty	(slight, low, …)	5–24%
xxx.2	MODERATE difficulty	(medium, fair, …)	25–49%
xxx.3	SEVERE difficulty	(high, extreme, …)	50–95%
xxx.4	COMPLETE difficulty	(total, …)	96–100%
xxx.8	Not specified		
xxx.9	Not applicable		

ICF: International Classification of Functioning, Disability, and Health.

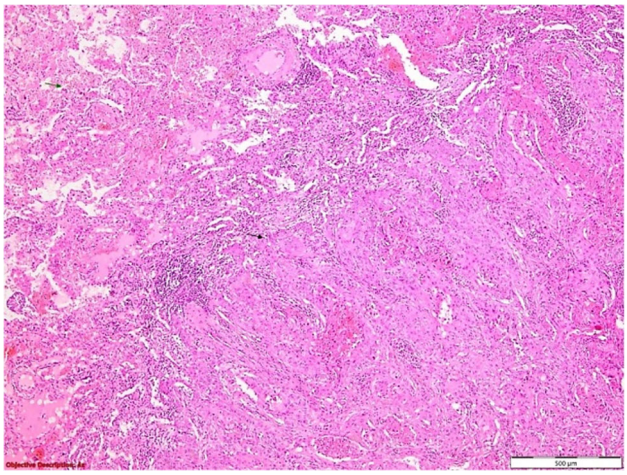

Figure 2 – ***Lung tissue (→) infiltrated by sheets of neoplastic epithelial cells exhibiting histopathological features characteristic of keratinizing squamous cell carcinoma (→). Hematoxylin–Eosin (HE) staining, 40×.***

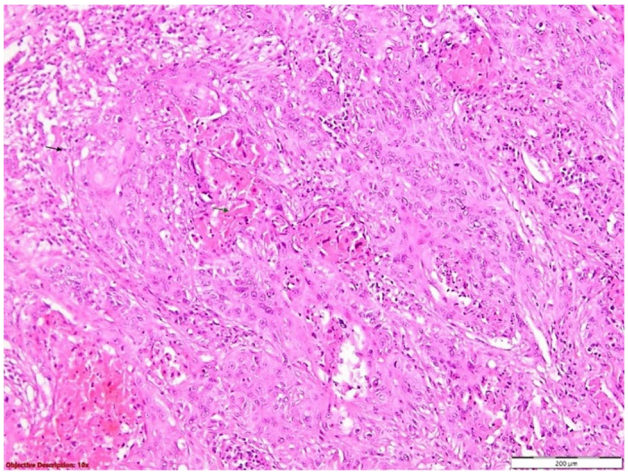

Figure 3 – ***Squamous cell carcinoma (→) composed of large, polygonal cells with vesicular nuclei, abundant eosinophilic cytoplasm and keratin pearl (→) formation. HE staining, 100×.***

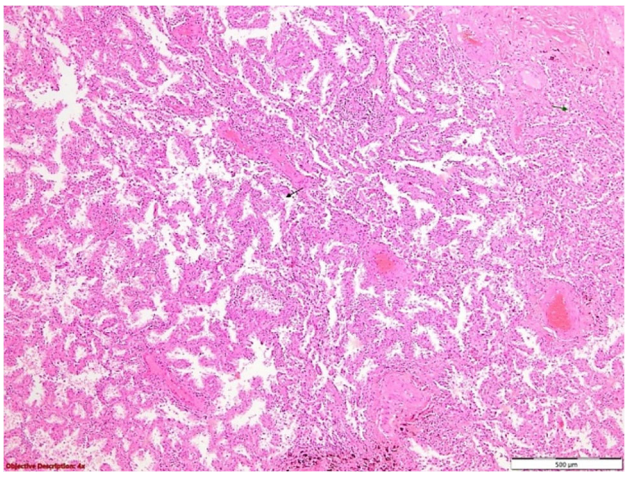

Figure 4 – ***Lung parenchyma (→) infiltrated by adenocarcinoma (→) composed of large malignant cells exhibiting moderate nuclear pleomorphism. HE staining, 40×.***

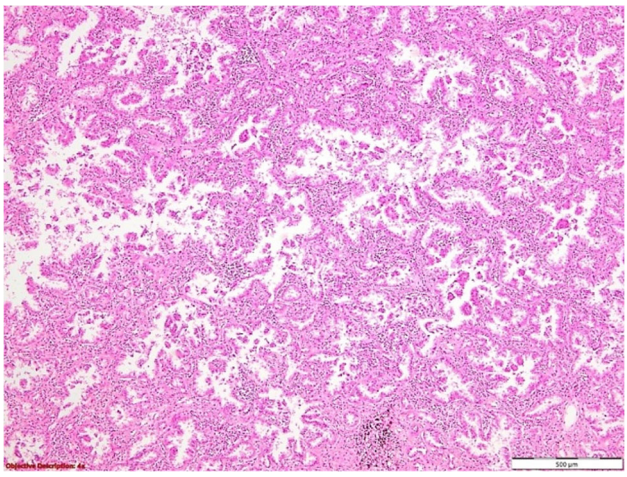

Figure 5 – ***Adenocarcinoma exhibiting a polymorphous architectural pattern, characterized by the coexistence of micropapillary, acinar and papillary growth structures. HE staining, 40×.***

Additional immunohistochemical (IHC) staining and molecular testing were conducted to identify key diagnostic and therapeutic biomarkers. These included *EGFR* mutations, PD-L1 expression using standardized IHC assays, and ALK rearrangements assessed by either IHC or fluorescence *in situ* hybridization (FISH), depending on availability. These markers were applied to confirm diagnosis and guide treatment decisions in accordance with current clinical guidelines for lung cancer.

Data analysis

Data are presented as mean ± standard deviation (SD) for continuous variables and count of individuals for categorical variables. The correlation between different variables was evaluated using the following methods: categorical *vs.* continuous – analysis of variance (ANOVA) test; continuous *vs.* categorical – Kruskal–Wallis' test; continuous *vs.* continuous – Pearson's coefficient; categorical *vs.* categorical – χ^2 (*chi*-squared) test.

A p-value <0.05 was considered statistically meaningful.

Statistical analyses were conducted using Statistical Package for Social Sciences (SPSS) 29 (2022) for Windows 10 (SPSS Inc., Chicago, IL, USA) and applied according to the current methodology.

Results

Based on the established inclusion and exclusion criteria, a total of 62 patients (n=44 F, n=18 M) diagnosed with NSCLC were enrolled in the study, consisting of individuals with confirmed adenocarcinoma or SCC subtypes. Biomarker analysis identified the presence or absence of ALK, EGFR, and PD-L1 expression, and patients underwent comprehensive functional evaluation using the ICF–RCS, 6MWD test, EORTC QLQ-C30 questionnaire, and GAD-7 anxiety scale.

We began by examining potential correlations between *EGFR* mutation status and functional outcomes, including the 6MWD, anxiety levels measured by the GAD-7 scale, and health-related QoL assessed using the EORTC QLQ-C30 questionnaire. Nevertheless, no statistically meaningful associations were identified between EGFR and any of these measures.

We also explored potential correlations between PD-L1 expression and functional outcomes, including 6MWD, anxiety levels assessed by the GAD-7 questionnaire, and health-related QoL as measured by the EORTC QLQ-C30. Similar to EGFR, no statistically meaningful associations were noted between PD-L1 expression and any of these variables.

In contrast, *ALK* mutation status was meaningfully associated with anxiety levels, as measured by the GAD-7 questionnaire (p=0.038), with ALK-positive patients showing higher anxiety scores, suggesting a potential connection between this genetic alteration and higher emotional distress (Figure 6). Nevertheless, no significant associations were found between ALK and the 6MWD or the EORTC QLQ-C30.

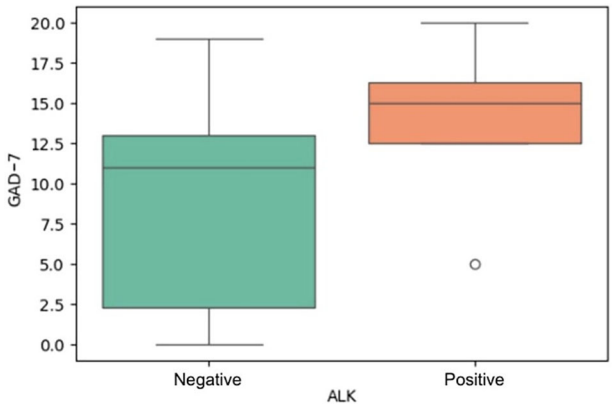

Figure 6 – ***Generalized Anxiety Disorder 7-item (GAD-7) vs. anaplastic lymphoma kinase (ALK).***

We began by examining potential correlations between *EGFR* mutation status and selected indicators from the ICF–RCS. The ICF domains assessed included body functions – b130 (energy and drive functions), b152 (emotional functions), b280 (sensation of pain), and b455 (exercise tolerance functions); activities – d450 (walking) and d640 (doing housework); participation – d230 (carrying out daily routine) and d920 (recreation and leisure); and environmental factors – e110 (products or substances for personal consumption), e115 (products and technology for personal use in daily living), and e120 (products and technology for personal indoor and outdoor mobility and transportation). While exploratory correlations were assessed between *EGFR* status and these functional domains, no statistically meaningful associations were found.

We also explored potential relationships between PD-L1 expression and the same outcome measures. Similar to EGFR, no statistically meaningful associations were noted between PD-L1 and any ICF-based functional indicators.

In contrast, analysis of *ALK* mutation status revealed a statistically meaningful association with the b152 domain (emotional functions) (p=0.022), suggesting a possible link between this genetic alteration and emotional functioning (Figure 7). No other significant associations were found between ALK and the remaining ICF domains.

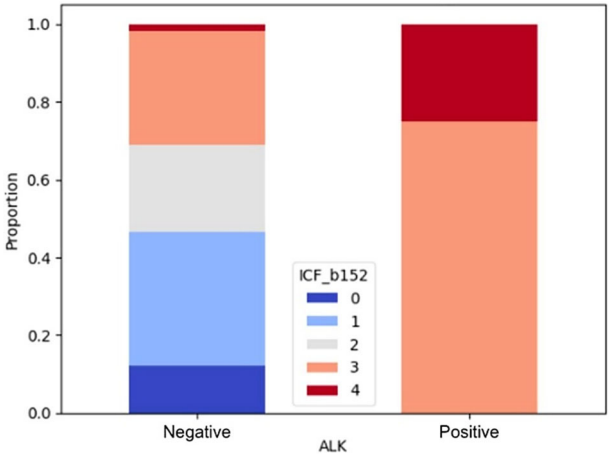

Figure 7 – ***ICF_b152 vs. ALK. ICF_b152: "Emotional functions" category within the World Health Organization (WHO) International Classification of Functioning, Disability and Health (ICF).***

Discussions

This original study explores functional quantification in patients with bronchopulmonary cancer, focusing on correlations between key biomarkers (PD-L1, EGFR, and ALK) and functional profiles in the context of PR. Functional outcomes were evaluated using the ICF–RCS, along with the 6MWD test for exercise capacity, the EORTC QLQ-C30 for health-related QoL, and the GAD-7 for anxiety.

In our study group, patients presented notable functional limitations at the start of rehabilitation, reflected by moderate impairments across multiple ICF–RCS domains and reduced 6MWD performance. QoL, as measured by the EORTC QLQ-C30, revealed lower physical functioning, lower global health status, and compromised role functioning – patterns consistent with the symptom burden typically observed in lung cancer. These results reinforce the clinical

value of rehabilitation-based assessments even before treatment-related decline becomes evident.

Similar improvements in functional capacity and symptom burden have been reported in patients with chronic respiratory diseases, particularly chronic obstructive pulmonary disease, where structured PR programs have been shown to significantly enhance exercise tolerance, reduce dyspnea, and improve health-related QoL, as demonstrated across multiple studies [22–24].

A significant association was identified between *ALK* mutation status and the ICF domain b152 (emotional functions), as well as anxiety levels assessed by the GAD-7 questionnaire. These results suggest that *ALK* mutations may influence not only tumor biology and treatment response but also emotional well-being and functional recovery in NSCLC patients. No significant associations were found between PD-L1 or EGFR expression and any of the functional or psychological outcomes measured in the present study.

The absence of correlations for PD-L1 and EGFR aligns with existing literature, which offers limited direct evidence linking these biomarkers to ICF-defined domains, 6MWD performance, GAD-7 scores, or EORTC QLQ-C30 results. While some studies report improved health-related QoL in *EGFR*-mutant patients treated with TKIs, these focus on therapeutic outcomes rather than baseline functional status [25, 26]. Similarly, PD-L1 studies emphasize treatment response [27], with little investigation into psychological or functional domains. As such, the present study contributes novel insights by linking *ALK* mutation status with both functional and emotional outcomes, highlighting a gap in current research.

Although data specifically exploring *ALK* mutations and functional or mental health outcomes are limited, existing research provides important context. ALK-positive NSCLC patients are often younger and more likely to be non-smokers, factors that may influence psychosocial burden and recovery patterns. The STRESS-LUNG study found that nearly half of patients with advanced NSCLC experienced clinically significant emotional distress, which was associated with poorer survival [28]. This aligns with our observation that *ALK* status may be linked to emotional vulnerability during rehabilitation.

In addition, real-world studies indicate that ALK inhibitors can offer clinical benefits even in patients with poor performance status, suggesting possible improvements in functional capacity within this subgroup [29]. These therapeutic effects may partly explain the differences in functional outcomes observed among ALK-positive patients.

The ICF–RCS proved to be a useful and accessible tool for evaluating functional status, offering added value in NSCLC where traditional measures like pulmonary function tests may not fully capture patient experience. By connecting *ALK* mutation status with functional and emotional assessment, our results support a more integrated approach to care.

The GAD-7 also demonstrated utility in this population. Prior research shows that about 30% of lung cancer patients report significant anxiety using this tool [30]. The association we observed between *ALK* status and GAD-7 scores suggests that genetic testing could help identify patients at risk for anxiety, enabling earlier psychological support.

Additional characteristics of our group further support the study's feasibility. Patient compliance was high, potentially influenced by the predominance of women, who often engage more consistently in healthcare interventions. Participants had normal BMI values, which facilitated the implementation of the rehabilitation program and successful completion of the 6MWD test. The two main histological subtypes – adenocarcinoma and SCC – were represented in nearly equal proportions, with a slight predominance of adenocarcinoma, consistent with epidemiological trends reported in published evidence [31].

Study limitations

Despite its contributions, the present study has limitations. The group size was relatively small, and its cross-sectional design limits causal interpretations. Conducted at a single center, the generalizability of findings may also be constrained. Nonetheless, our results highlight the importance of integrating biological, functional, and psychological assessments in NSCLC care. Further research with larger, more diverse cohorts and longitudinal designs are needed to validate these results and guide more individualized rehabilitation strategies. Future research should investigate whether specific biomarker profiles can predict how much patients improve functionally during PR. Additionally, longitudinal studies are needed to determine if early integration of biomarker assessment into rehabilitation planning can support patients' progress over time. Expanding this approach across various medical centers may also clarify its applicability and strengthen its relevance for routine clinical practice.

Conclusions

This study identified a significant link between *ALK* mutation status and the ICF domain b152, which reflects emotional functions, as well as a related association with anxiety levels as assessed by the GAD-7 questionnaire. These findings suggest that genetic alterations like *ALK* mutations may have an impact not only on tumor behavior and treatment pathways but also on the emotional health of patients with NSCLC. Recognizing these associations underscores the need to include emotional and functional domains in routine patient assessment during clinical care.

In contrast, no clear associations were found between PD-L1 or EGFR expression and any of the functional or psychological outcome measures applied in this study, including the ICF framework, 6MWD, EORTC QLQ-C30, and GAD-7. This observation is consistent with the current literature, which offers limited evidence connecting these biomarkers to domains of functioning or mental health. It highlights the importance of future studies that examine how molecular characteristics may influence patients' functional abilities and overall health-related QoL, beyond traditional treatment outcomes.

Bringing together molecular characteristics with emotional and functional assessments may provide a deeper and more accurate understanding of patient needs – particularly in the context of rehabilitation, where personalized strategies are essential. Including such factors in routine clinical evaluations could support more effective, personalized care strategies aimed at improving both physical recovery and emotional resilience in NSCLC patients.

Looking ahead, larger studies with diverse populations and longitudinal follow-up are needed to confirm these preliminary findings and to better understand the practical applications of molecular-functional associations. Ultimately, this line of research has the potential to improve the quality and precision of supportive care in lung cancer, moving toward a more integrative model that addresses both medical and psychosocial aspects of long-term patient outcomes.

Conflict of interests

The authors declare no conflict of interests.

Informed Consent Statement

All participants in the study provided informed consent.

Statement of Human and Animal Rights

This prospective observational study was conducted in accordance with the Declaration of Helsinki and approved by both institutional Ethics Committees: Approval No. 91/19.02.2024 (University of Medicine and Pharmacy of Craiova, Romania); Approval No. 23361/17.10.2023 (Marius Nasta Institute of Pneumophthisiology, Bucharest, Romania).

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