Original Article

Effects of Aerobic Exercise on The Six Minutes Walking Test and Quality of Life in EGFR Mutation Non-Small Cell Lung Cancer Patients

Lia Priscilia, Ana Rima Setijadi, Hendrastutik Apriningsih, Ahmad Farih Raharjo, Harsini, Yusup Subagio Sutanto

Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Sebelas Maret, Dr. Moewardi General Regional Hospital, Surakarta, Indonesia

Abstract

Background: Lung cancer reduces lung function, muscle mass, and psychological well-being, which lowers exercise capacity and quality of life. Pulmonary rehabilitation, such as aerobic exercise, can improve exercise capacity and the quality of life (QoL) in lung cancer patients. This study aimed to investigate the influence of aerobic exercise on the six-minute walking test (6MWT) and the quality of life of lung cancer patients.

Methods: A clinical trial with a quasi-experimental, pretest, and post-test design was conducted on stage ≥IVa adenocarcinoma lung cancer patients who were receiving outpatient targeted therapy at the pulmonary clinic of Dr. Moewardi General Hospital for ≥1 month starting from May 2023, until the required sample size was met. The 6MWT and Functional Assessment of Cancer Therapy-Lung (FACT-L) were measured at the baseline and eight weeks ±2 weeks after aerobic exercise by walking about 15-20 minutes and breathing exercises.

Results: The study included fourteen patients in the control group and fifteen patients in the aerobic group. The mean difference of 6MWT between the control and the aerobic group was 38.33 m. Functional, lung cancer subscale (LCS), total, and TOI in FACT-L showed significant differences in the increment pre-test and post-test between the control and aerobic group ($P<0.05$), with significant differences in pre-test and post-test of most categories in both groups, except for social.

Conclusion: Aerobic exercise, psychological support, and nutrition have significantly improved the 6MWT and quality of life in lung cancer patients.

Keywords: 6MWT, adenocarcinoma, aerobic exercise, FACT-L, quality of life

Corresponding Author:
Lia Priscilia | Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Sebelas Maret, Dr. Moewardi General Regional Hospital, Surakarta, Indonesia | prisciliasibarani@gmail.com

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INTRODUCTION

Lung cancer is the leading cause of cancer-related death worldwide, with a five-year survival rate of 10–20%.[1] In the United States, nearly two million new cases and 700,000 deaths were estimated in 2022.[2] Staging of malignancy has a significant impact on survival rates, which range from 92% in early stages to fewer than 1% in advanced stages. Quality of life and life expectancy for lung cancer patients are heavily affected by the severity of the disease and the symptoms they experience.[2,3]

Respiratory complaints in nearly 90% of patients can reduce their quality of life, increase stress, limit daily activities, exercise capacity, and physical function.[4] Early detection and a multidisciplinary approach improve outcomes for lung cancer patients.[5] The primary goal in late-stage lung cancer is to reduce patient complaints and enhance their quality of life.[2] The Quality of Life Questionnaire and Lung Cancer Module (QLQ-LC13) and Functional Assessment of Cancer Therapy-Lung (FACT-L) are the most commonly used tools worldwide to assess quality of life in lung cancer.[6]

The success of lung rehabilitation programs in chronic obstructive pulmonary disease (COPD) has intrigued clinicians to see the impact in lung cancer.[7] Pulmonary rehabilitation uses a multidisciplinary approach and aims to improve symptoms, physical activity, and quality of life.[8] It involves education, physical exercises tailored to patients' needs and preferences, and behavior change to health-enhancing behaviors.[8]

The goal of physical exercises such as aerobics is to maintain an active lifestyle, physical fitness, fatigue control, and overall QoL of patients with lung cancer.[9] There are several studies that show the benefits of exercises like aerobics, inspiratory muscle training, resistance, and a combination of them in lung cancer. However, research on the impact of aerobic exercise on lung cancer patients is relatively limited.

This study evaluates how aerobic exercise can impact the six-minute walk test (6MWT) and quality of life in patients with lung cancer with FACT-L. The aim is to provide insights into the role of aerobic exercise for lung cancer patients, offering a simple and practical approach that can be easily implemented by the patients themselves. Research in aerobics for lung cancer itself has been limited in the past decade, making this study a valuable addition to the field.

METHODS

This study used a quasi-experimental pre-post design. It was conducted in May 2023 at Dr. Moewardi General Hospital, Surakarta, involving all research subjects. Consecutive sampling was used, with each eligible patient becoming a research subject.

The 6MWT and FACT-L were measured at first and after eight weeks ±2 weeks. Intervention in the study is regular aerobic exercise, such as walking about 15–20 minutes, which is recorded by the patients' family and sent to researchers regularly.[10] Both control and aerobic groups included stage ≥IVa lung adenocarcinoma patients receiving targeted therapy with tyrosine kinase inhibitor (TKI) for at least one month since May 2023, confirmed by specialists and histopathological findings.

Patients eligible for this study had an Eastern Cooperative Oncology Group (ECOG) performance status <2, age ≥18, proficiency in reading and writing in Indonesia, have no history in regular physical exercise for >1 month, have a family member or guardian for exercise supervision, and able to use handphone to facilitate communication. All patients should follow nutritional guidelines, commit to the research, and provide informed consent. Patients in the aerobic group should start aerobic exercise by walking and breathing exercises as a routine, while the control group can do regular breathing exercises.

The exclusion applies to patients with bone metastases, brain metastases, heart conditions impeding physical exercise, hemoglobin <10 g/dL, platelets <100.000 /µL, pneumonia symptoms, BMI <16 kg/m^2, or other conditions interfering with the study. Patients were also excluded if they performed aerobic exercise less than 60% of the time or ≤2 times per week during the program.

To compare 6MWT and FACT-L scores between groups, unpaired t-tests or Mann-Whitney tests were used based on data normality. Within-group pre-post comparisons used paired t-tests or Wilcoxon tests accordingly.

RESULTS

A total of 57 outpatients with stage ≥Iva adenocarcinoma undergoing targeted therapy were identified between May and early July, with 34 patients meeting the inclusion criteria. Two patients died, and three patients were lost to follow-up, resulting in 29 subjects participating until the end. The study subjects were divided into a control group comprising 14 patients and an aerobic group consisting of 15 patients.

Most of the patients were under 65 years old and were females in both groups. The majority of patients had an elementary school education. Most patients had never smoked. Stage IVB was the most common cancer stage. Exon 19 deletion was prevalent in both groups. The primary therapy was afatinib in most cases, with a median therapy duration of 4.5 and 9 months in the control group and aerobic group, respectively. Complete data is provided in Table 1.

Table 2 shows pre-test 6MWT results for the control and aerobic groups. Data were not normally distributed (P<0.05), so the Mann-Whitney test was used. Median 6MWT for the control group was 245.00m (range=180.00–360.00m), meanwhile the aerobic group was 280.00m (range=200.00–350.00m). No significant difference in pre-test 6MWT (P=0.17).

Table 1. Sample characteristics

Characteristic	Group		P
	Control (n=14)	Aerobic (n=15)	
Age			
<65 years	11 (37.9%)	11 (37.9%)	0.542[a]
>65 years	3 (10.3%)	4 (13.8%)	
BMI			
Underweight	7 (24.1%)	6 (20.7%)	0.438[b]
Normal	4 (13.8%)	8 (27.6%)	
Overweight	2 (6.9%)	1 (3.4%)	
Obesity I	1 (3.4%)	0 (0.0%)	
Sex			
Female	10 (34.5%)	11 (37.9%)	0.617[a]
Male	4 (13.8%)	4 (27.6%)	
Education			
Primary School	8 (27.6%)	7 (24.1%)	0.479[b]
Junior High School	2 (6.9%)	1 (3.4%)	
Senior High School	4 (13.8%)	5 (17.2%)	
Not going to school	0 (0.0%)	2 (6.9%)	
Occu-pation			
Workers	2 (6.9%)	2 (6.9%)	0.850[b]
Housewife	3 (10.3%)	2 (6.9%)	
Merchant	3 (10.3%)	2 (6.9%)	
Farmer	3 (10.3%)	6 (20.7%)	
Self-employed	3 (10.3%)	3 (10.3%)	
Smoking History			
No Smoking	7 (24.1%)	11 (37.9%)	0.196[b]
Smoking	7 (24.1%)	4 (13.8%)	
Staging			
IVA	2 (6.9%)	0 (0.0%)	0.224[a]
IVB	12 (41.4%)	15 (51.7%)	
Mutation			
Exon 19 deletion	12 (41.4%)	13 (44.8%)	0.674[a]
Exon 21 L858R	2 (6.9%)	2 (6.9%)	
Therapy Agent			
Afatinib	13 (44.8%)	14 (48.3%)	0.367[b]
Erlotinib	1 (3.4%)	0 (0.0%)	
Gefitinib	0 (0.0%)	1 (3.4%)	
Therapy duration	4.5 (2–29)	9 (2–25)	0.272[c]

Note: [a]Fisher exact test; [b]chi-square; [c]Mann-Whitney test

Most pre-test FACT-L data were normally distributed for various categories, allowing unpaired t-tests with equal variance. Lung cancer subscale (LCS) category used Mann-Whitney due to non-normal distribution. In most categories, mean differences between control and aerobic groups weren't statistically significant (P>0.05). In summary, there are no significant differences in the baseline characteristics of all subjects.

Normality tests and Levene's test indicate that the data are normally distributed and have equal variances. An unpaired t-test with equal variance was used. A significant mean difference of 38.33 meters was observed between the control and aerobic groups (P=0.001), with a 95% confidence interval (CI) of 16.73 to 59.94. See Table 3 for details on the pre-test and post-test 6MWT increment (Δ).

Table 4 shows that the control group's pre-test and post-test 6MWT data are normally distributed, with a significant mean difference of 20.00 meters (P=0.013; 95% CI=5.06–34.94). In contrast, the aerobic group's data is not normally distributed, leading to the use of a non-parametric Wilcoxon test. The aerobic group shows a significant mean difference in pre-test-post-test 6MWT (P=0.001), with all post-test values being higher than pre-test values.

The difference (Δ) of pre-test-post-test between the control group and aerobic group in Table 5 shows significantly greater improvements in some categories, such as functional (P=0.0001), LCS (P=0.001), total (P=0.004), and TOI (P=0.024).

Table 2. Variables characteristic

Characteristic	Group		Mean Difference	P	95% CI
	Control (n=14)	Aerobic (n=15)			
Pre-test 6MWT (m)[a]	245.00 (180.00–360.00)	280.00 (200.00–350.00)	---	0.17	---
Pre-test FACT-L					
Physical[b]	16.07±4.96	18.93±4.68	2.86	0.122	−0.82–6.54
Social[b]	17.79±4.40	18.93±4.00	1.15	0.469	−2.06–4.35
Emotional[b]	18.57±4.32	20.93±3.12	2.36	0.102	−0.50–5.22
Functional[b]	15.57±4.53	17.40±4.82	1.83	0.303	−1.75–5.40
LCS[a]	21.50 (14.00–24.00)	21.00 (17.00–28.00)	---	0.219	---
Total[b]	88.14±17.17	98.47±14.19	10.32	0.088	−1.65–22.29
TOI[b]	54.00±10.96	60.13±8.14	6.13	0.097	−1.19–13.45
FACT-G[b]	68.00±14.45	76.20±12.68	8.20	0.115	−2.15–18.55

Note: [a]Mann-Whitney test; [b]independent T-test; 95% CI=95% Confidence Interval; LCS=lung cancer subscale; FACT-G=functional assessment of cancer therapy-general; TOI=trial outcome index

Table 3. The difference in the pre-test to post-test difference of the Six Minutes Walking Test between the control and aerobic groups.

6MWT[a]	Control (n=14)	Aerobic (n=15)	Mean Difference	*P*	95% CI
Δ Pre test- post test (meters)	25.87±25.86	58.33±30.45	38.33	0.001*	16.73–59.94

Note: [a]independent T-test; 6MWT=six minutes walking test; *significant if *P*<0.05; 95% CI=95% Confidence Interval; Δ=increment

Table 4. The difference in pre-test and post-test results of the Six-Minute Walking Test between the control group and the aerobic group.

Group	6MWT		Mean Difference	*P*	95% CI
	Pre test	Post test			
Control[a]	242.14±42.41	262.14±49.18	20.00	0.013*	5.06 – 34.94
Aerobic	280.00 (200.00–350.00)	320.00 (280.00–410.00)	---	0.001*	---

Note: [a]paired t-test; [b]Wilcoxon text; *significant if *P*<0.05; 6MWT=six minutes walking test

Table 5. The comparison of the pre-test - post-test FACT-L score difference between the control group and aerobic group.

FACT-L[a]	Δ *Pre test-Post test result*		*P*
	Control (n=14)	Aerobic (n=15)	
Physical	3.00 (-1.00 – 9.00)	2.00 (1.00 – 9.00)	0.895
Social	0.00 (-2.00 – 2.00)	0.00 (0.00 – 3.00)	0.165
Emotional	0.00 (0.00 – 200)	0.00 (0.00 – 3.00)	0.900
Functional	1.00 (-2.00 – 2.00)	4.00 (0.00 – 8.00)	0.000*
LCS	1.50 (0.00 – 2.00)	4.00 (0.00 – 10.00)	0.001*
Total	6.50 (-1.00 – 14.00)	9.00 (6.00 – 30.00)	0.004*
TOI	4.50 (-1.00 – 12.00)	7.00 (1.00 – 21.00)	0.024*
FACT-G	5.50 (-1.00 – 12.00)	6.00 (4.00 – 20.00)	0.095

Note: [a]Mann-Whitney; *significant if *P*<0.05; FACT-L=functional assessment of cancer therapy-lung; LCS=lung cancer subscale; FACT-G=functional assessment of cancer therapy-general; TOI=trial outcome index; 95% CI=95% Confidence Interval; Δ=increment

Table 6. The difference in pre-test and post-test FACT-L results in the control group and aerobic group.

FACT-L	Result		Mean Difference	P	95% CI
	Pre-test	Post test			
Physical					
Control[a]	16.07±4.97	19.57±3.72	3.50	0.0001*	1.87 – 5.13
Aerobic[a]	18.93±4.68	22.93±3.45	4.00	0.0001*	2.28 – 5.71
Social					
Control[b]	17.00 (10.00 – 25.00)	17.00 (10.00 – 25.00)	---	0.785	---
Aerobic[b]	19.00 (12.00 – 27.00)	20.00 (15.00 – 27.00)	---	0.039*	---
Emotional					
Control[b]	19.00 (10.00 – 24.00)	19.50 (11.00 – 24.00)	---	0.020*	---
Aerobic[b]	21.00 (16.00-28.00)	23.00 (17.00-28.00)	---	0.020*	---
Functional					
Control[b]	15.00 (9.00-22.00)	20.00 (10.00-27.00)	---	0.025*	---
Aerobic[a]	17.40±4.82	18.20±4.16	3.87	0.000*	2.55 – 5.19
LCS					
Control[b]	21.50 (14.00-24.00)	25.50 (16.00-28.00)	---	0.001*	---
Aerobic[a]	22.27±3.41	23.47±4.16	4.13	0.000*	2.70 – 5.57
Total					
Control[a]	88.14±17.17	100.50±12.55	6.43	0.000*	4.07 – 8.79
Aerobic[b]	97.00 (73.00 – 119.00)	107.00 (88.00 – 132.00)	---	0.001*	---
TOI					
Control[a]	54.00±10.96	60.86±7.60	5.00	0.000*	3.08 – 6.92
Aerobic[b]	59.00 (42.00 – 76.00)	65.00 (56.00 – 78.00)	---	0.001*	---
FACT-G					
Control[a]	68.00±14.46	76.07±11.35	5.00	0.000*	2.84 – 7.16
Aerobic[b]	74.00 (55.00 -96.00)	83.00 (70.00 – 106.00)	---	0.001*	---

Note: [a]Paired t-test; [b]Wilcoxon test; *significant if *P*<0.05

Normality tests in Table 6 revealed that paired t-tests were used for normally distributed data, while Wilcoxon tests were used for not normally distributed data. Table 6 shows a significant difference in pre-test-post-test scores in most of the categories of FACT-L, either in the control and aerobic group (*P*<0.05; 95% CI does not contain zero) except for the social domain (*P*=0.785). All FACT-L categories in the aerobic group showed significant differences between pre-test and post-test scores (*P*<0.05). Notably, post-test scores in total, FACT-G, and TOI were consistently higher than pre-test scores.

DISCUSSION

This study included 34 patients out of a total of 57 stage ≥IVa adenocarcinoma lung cancer patients in the targeted therapy due to various factors such as patient unwillingness and failure to meet inclusion criteria, such as illiteracy, lack of caregiver supervision, and physical limitations hindering exercise. The total number of patients who completed the study was 29, with 14 patients in the control group and 15 patients in the aerobic group.

The characteristics of the research subjects in Table 1 indicate a predominance of subjects under the age of 65, females, a history of non-smoking, and EGFR exon 19 deletion mutation. EGFR mutations in lung adenocarcinoma are more commonly found in Asians (38.8–64%), females, non-smokers or light smokers, with nearly 90% of all mutations being exon 19 deletions and L858R mutations in exon 21.[3,11,12] Characteristics of the research subjects in Yoon et al study in South Korea, which included 388 patients, found that more women suffer from lung adenocarcinoma across a wide range of ages.[12]

Non-smoking lung adenocarcinoma patients are more frequently found in women under 60 years of age due to differences in mutations between smoking and non-smoking patients. EGFR and echinoderm microtubule-associated protein-like 4-anaplastic lymphoma kinase (EML4-ALK) mutations are more commonly associated with carcinogenesis in non-smoking patients, while Kirsten rat sarcoma (KRAS), retinoblastoma (RB), and p53 mutations are more frequently found in smoking patients.[3]

The majority of targeted therapies involved afatinib in 27 patients, followed by erlotinib and gefitinib. Afatinib is a second-generation TKIs that irreversibly binds EGFR and is effective against the T790M exon 20 mutation, which is typically resistant to first-generation TKIs.[11] The LUX-Lung 7 study by Park et al showed that second-generation TKIs have a potentially superior effect, though not statistically significant, but are associated with more frequent and severe side effects.[13]

The mean difference between pre-test and post-test 6MWT in the control and aerobic groups was 38.33 meters, signifying statistical significance (*P*=0.001). The control group showed a statistically significant mean difference of 20 meters in the pre-test to post-test 6MWT (*P*=0.013), while the aerobic group exhibited a significant difference of 40 meters (*P*=0.01).

These findings align with previous studies. For instance, Jones et al reported a 40-meter increase in 6MWT for advanced-stage lung cancer patients undergoing physical exercise, which improved prognosis. Wang et al showed a non-significant 12-meter improvement in KPKBSK patients and a significant 20-meter improvement in KPKBSK patients with COPD.[14] Other research by Hwang et al highlighted that aerobic exercise in adenocarcinoma patients significantly increased exercise capacity assessed by VO_2.[15]

Physical exercise induces physiological angiogenesis by releasing VEGF in skeletal muscles without involving HIF-1α, which is associated with abnormal angiogenesis in cancer. It also activates various factors, such as p53, IL6 myogenic, and inhibits the expression of TNF-α, GLUT4, and HK2, playing roles in regulating oncogenesis processes.[9,16] Exercise increases lactate levels, thereby reducing pH, which hinders T-cell activity and cell proliferation that contributes to oncogenesis.[9]

This study found a significant difference in mean scores between pre-test and post-test FACT-L in the functional, LCS, total, and TOI categories, with values of *P*<0.05 and 95% confidence intervals that do not include zero. This aligns with prior research indicating a direct relationship between improved quality of life and routine walking activities.[17] The study also corresponds with systematic reviews showing that physical exercise significantly enhances quality of life, leading to improved oxygen consumption, confidence, physical function, fatigue threshold, and social function.[18] While some studies, like Egegaard et al and Dhillon et al, reported no significant differences in FACT-L scores between intervention and control groups, the general trend suggests positive outcomes from aerobic exercise.[19,20]

Fatigue in cancer patients, encompassing factors such as frailty, sleep disturbances, and reduced concentration, negatively impacts various aspects of life, including work, mood, social relationships, and overall quality of life.[21] Cancer-related fatigue may involve inflammation, anemia, HPA axis disruption, serotonin imbalance, and impaired ATP production play a crucial role. Physical exercise helps regulate these processes and reduce cancer-related fatigue, ultimately improving symptom severity and enhancing the quality of life for cancer patients.[21,22]

Studies, such as El-kader et al, show that aerobic exercise decreases inflammation, enhances cardiorespiratory function, and reduces markers associated with inflammation and endothelial dysfunction. Additionally, it improves metabolism, alleviates pain and muscle stiffness, and enhances physical recovery. Aerobic exercise simultaneously enhances environmental and internal stress regulation, reduces stress levels, and mitigates fatigue, discomfort, and negative emotions, ultimately improving the overall quality of life for lung cancer patients.[22]

LIMITATION

The variation in staging and systemic therapies limits the generalizability of aerobic exercise outcomes in this study. The gold standard for assessing functional capacity is a measurement of VO_2 peak using CPET, which is currently unavailable at Dr. Moewardi General Hospital. Therefore, the 6MWT serves as a suitable alternative to significantly measure exercise capacity, and it is easy to implement. Exercise options were limited due to patient comorbidities, which narrowed the scope of this research on the benefits of physical exercise for exercise capacity and the quality of life of patients.

CONCLUSION

Aerobic exercise improves the 6-minute walk test and quality of life in lung cancer patients. Future studies should explore different lung cancer subtypes, treatment modalities, and exercise approaches. Aerobic exercise can enhance the quality of life for stable outpatient lung cancer patients without walking impairments. Further studies can explore its impact on patient well-being and survival.

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CONFLICT OF INTEREST

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