Combined Upper Limb Exercise and Creatine Monohydrate Supplementation Improved Musculoskeletal Function in NSCLC Patients

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Abstract

Background: Lung cancer is a chronic respiratory disease that causes muscle dysfunction. Giving creatine monohydrate supplementation combined with exercise has efficacy in increasing lean body mass (LBM), muscle strength, and physical function. This study aims to analyze the effect of a combination of creatine monohydrate supplementation and upper limb exercise on skeletal muscle dysfunction in NSCLC patients.

Methods: A quasi-experimental study with a pretest-posttest study on NSCLC patients given epidermal growth factor receptor (EGFR) – tyrosine kinase inhibitors (TKIs) from outpatient at RSUD Dr. Moewardi Surakarta in September - October 2021. The combination group of creatine monohydrate supplementation with upper limb exercise (n=15), the group with creatine monohydrate supplementation only (n=16), and the control group (n=15). Lean body mass in kilograms and percentages, 6-minute walk test (6MWT), and quality of life were assessed after 8 weeks of treatment.

Results: The increase in LBM in the combination group was 4.22±1.81kg and 6.38±2.48% (*P*=0.0001). The combination groups have a greater increase in the 6MWT was 104±20.07 meters. The increase in quality of life in the combined creatine monohydrate supplementation group with upper limb exercise was 20.80±10.75. Changes in the value of LBM, 6MWT, and quality of life (QoL) in the creatine monohydrate supplementation combined with upper limb exercise were significantly different compared to the creatine monohydrate supplementation only group and the control groups.

Conclusion: There is a greater effect of giving a combination of creatine monohydrate supplementation and upper limb exercise on LBM, 6MWT, and QoL in NSCLC patients.

Keywords: 6MWT, creatine, exercise, LBM, NSCLC, QoL

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INTRODUCTION

New cases of lung cancer in Indonesia increased more than five times in the last ten years.[1,2] Most patients with NSCLC adenocarcinoma-type have sensitization mutation in exon 19 or 21 (about 45 and 40% of patients, respectively) that activates the tyrosine kinase domain in the EGFR receptor especially among Asians because it has a higher prevalence of EGFR mutations compared to Caucasians. The use of EGFR-TKI as a first-line treatment has shown a longer progression-free survival (PFS), improved health-related quality of life, and lower side effects treatment-related when compared with standard chemotherapy.[3]

Lung cancer is a chronic respiratory disease that causes impaired ventilation that causes physical inactivation. Cancer patients are exposed to various specific cancer factors that result in the loss of mass and function of muscle, like factor-related to tumor cancer therapy, malnutrition, lack of physical activity, age, and comorbidities. Compensation to reduce symptoms of shortness of breath and fatigue by reducing activity resulting in muscle atrophy so that the vicious cycle keeps progressing and explains the connection between physical inactivation and worsening of symptoms.[4,5] Muscle atrophy contributes to weakness, decreased mobility, and fatigue in cachectic patients and could increase the risk of respiratory failure as a common cause of death from cancer.

Cancer-related muscle dysfunction is defined as a measurable disturbance in muscle strength or muscle composition. The degree of muscle dysfunction can be measured from muscle strength and muscle composition in the form of lean body mass.[6,7] Upper extremity muscles are very important for manipulating objects and for personal care and affect the quality of life. Muscle strength also depends on muscle mass, length, innervation, size, and fiber type.[8]

Walking is a usual activity for all patients except for those with severe disorders. The American thoracic society (2002) recommends the 6-minute walk test to measure the response of therapeutic interventions for cardiorespiratory disease.[9]

Abnormalities of body composition affect all chronic lung diseases. Measuring body mass index (BMI) does not accurately reflect body composition changes like fat-free mass (FFM) which consists of bone, muscle, vital organs, and extracellular fluid. Lean body mass (LBM) differs from FFM in the form of lipid in the cellular membranes that are included in the LBM but only a small fraction or as much as 3–5% of the total body weight.[10,11]

Muscle mass is maintained by the balance between protein synthesis and breakdown, called protein turnover. Impaired ventilation due to lung cancer causes hypoxemia resulting in anaerobic metabolism. Lactate from anaerobic metabolism is increased and partially converted into glucose through the Cori cycle which requires adenosine triphosphate (ATP), causing a decrease in energy which results in muscle dysfunction. Muscle atrophy due to cancer occurs as a result of an increased inactivation of protein breakdown and suppression of protein synthesis.[12] Data on muscle mass were assessed by dual-energy X-ray absorptiometry (DXA) scan and bioelectrical impedance.

Creatine monohydrate (Cr) is one of the most researched supplements that has efficacy in increasing lean body mass, muscle strength, and physical function.[13,14] Creatine plays an important role to supply rapid energy during muscle contraction which involves the transfer of a phosphoryl group from phosphocreatine (PCr) to adenosine diphosphate (ADP) for regeneration of adenosine triphosphate (ATP) through a reversible reaction catalyzed by phosphocreatine kinase (PCK). Creatine is responsible for the transfer of energy from the mitochondria to the cytosol.[14–16]

Exercise training in chronic respiratory conditions is to optimize lung function in daily activities. The standard pulmonary rehabilitation protocol consists of three sessions of 30 to 90 minutes per week for 6 to 8 weeks consisting of individual aerobic exercise and strength training.[17,18]

Muscle strength resistance training involves specific muscle groups by lifting or pushing weights repeatedly. The American Thoracic Society/European Respiratory Society (ATS/ERS) for lungs rehabilitation recommend two set of 6–12 reps, gradually increased, a maximum of two to three times per week.[10,17,19]

Non-pharmacological modalities of therapy in lung cancer patients are still not widely studied. This study aims to determine the effect of the combination of creatine monohydrate supplementation and upper limb exercise in improving skeletal muscle dysfunction and improving the quality of life in NSCLC patients.

METHODS

Quasi-experiment studies with pretest and post-test control group designs were done to evaluate the lean body mass (kg), lean body mass (%), 6-minute walk test, and quality of life. The study was carried out at Dr. Moewardi Surakarta from September 2021 to November 2021. The study population was NSCLC patients with EGFR TKI at RSUD Dr. Moewardi Surakarta using consecutive sampling. The research subjects were grouped into the treatment group with the combination of creatine monohydrate supplementation with upper limb exercise as first group, creatine monohydrate supplementation only as second group, and the control group or third group. Subjects measured the lean body mass with a bioelectrical impedance scale, 6-minutes walking test, and quality of life using a Fact-L questionnaire.

The first group received an education on how to take creatine monohydrate supplementation and was taught about upper limb exercise. Creatine supplementation monohydrate as much as 5 grams (1 teaspoon) dissolved in 250 ml drinking water and consumed once a day. The upper limb exercise is carried out in a sitting position by holding a bottle filled with 600 mL of water then performing elbow flexion and extension movements to train the biceps and triceps muscles, abduction, and adduction movements of the upper arms to train the deltoids. The movement is continued by bending the body slightly then raising both hands and bringing them together behind the neck. The next movement is in a lying position and moving both hands ahead. Each set of movements is done for 12 repetitions and repeated up to 5 sets. Upper limb exercise sessions are carried out every day.

The supplementation group only received education on how to take the same amount of creatine monohydrate supplementation without giving upper limb exercise treatment. The control group was not given any non-pharmaceutical treatment. All forms of treatment are given every day for 8 weeks. Evaluation of lean body mass, 6-minute walk test, and quality of life were measured again after 8 weeks. The number of samples required is 15 samples per group.

Inclusion criteria of this study are stage IV NSCLC patients in hospital Dr. Moewardi Surakarta with targeted therapy for TKI EGFR at least on the second month, shows a minimum performance status (PS) of 70-80, the patient is willing to take part in the study by signing the informed consent, the patient's age is minimum 18 years, as well as patient, could read and write. The exclusion criteria of this study are patients with impaired consciousness, walking disorders, upper extremity activity disorders, and patients with pneumonia. The criteria for the discontinuity of the study where the subjects did not perform the procedure for 14 days consecutive.

This research was approved by the Ethics Worthiness Committee of the RSDM/Faculty of Medicine, Sebelas Maret University, Surakarta in October 2021. All research data were carried out by the normality test of the distribution of research data. All research data were tested for the normality of research data using the normality Kolmogorov-Smirnov test. The value of P>0.05 means that the subjects in the study are homogeneous. A difference test is a statistical technique test used to see the difference between treatment samples. Statistical tests on the pre and post-test independent samples were tested using a paired t-test if the data distribution was normal. If the data distribution is not normal then the Mann-Whitney test is used. The next difference test is ANOVA to see the difference among the three groups if the data distribution is normal. If the data distribution is not normal, then used the Kruskal-Wallis test. The difference test among the 3 groups was continued with the Bonferroni post hoc test if the data were homogeneous and Games-Howell if the data are non-homogeneous. The limit of the mean if the value of P≤0.05 means significant statistically.

RESULTS

This study was conducted at the Dr. Moewardi hospital Surakarta from September 2021 to October 2021. The eligible subjects were divided into three groups by consecutive sampling which is the combination group with creatine monohydrate supplementation with upper limb exercise, the group of creatine monohydrate supplementation only, and the control.

There are total 46 subjects recruited, but three of the subjects excluded due to death. Three subjects were discontinued in the study because the patient passed away. The subjects were then divided into 3 groups. The first group consisted of 15 NSCLC patients who received targeted therapy and creatine monohydrate supplementation combined with upper limb exercise. The second group consisted of 16 NSCLC patients who received targeted therapy and creatine monohydrate supplementation only. The third group was the control group, which consisted of 15 NSCLC patients who received targeted therapy. The research data collected were tabulated and then analyzed as follows.

Table 1. Characteristics of Subjects.

Characteristics	Group			P
	Group 1	Group 2	Group 3	
Sex				
Men	5 (10.9%)	5 (10.9%)	5 (10.9%)	0.99
Women	10 (21.7%)	11 (34.8%)	10 (21.7%)	
Age	60.7±7.43	58.1±8.16	53.1±14.17	0.135
Exon				
19	9 (19.6%)	10 (21.7%)	13 (28.3%)	0.213
21	6 (13%)	6 (13%)	2 (4.3%)	
Regimen targeted therapy				
Afatinib	11 (23.9%)	8 (17.4%)	8 (17.4%)	
Erlotinib	2 (4.3%)	3 (6.5%)	4 (8.7%)	0.611
Gefitinib	2 (4.3%)	5 (10.9%)	3 (6.5%)	
Duration therapy	10.4±9.62	11.06±6.77	13.27±9.03	0.631
Smoking history				
Smoker	3 (6.5%)	5 (10.9%)	4 (8.7%)	0.774
Non Smoker	12 (26.1%)	11 (23.9%)	11 (23.9%)	

Table 2. Characteristics of Variables

Variable	Group			P
	Group 1	Group 2	Group 3	
Lean body mass (pre) [kg]	34.0±7.16	32.23±6.33	36.53±9.55	0.313
Lean body mass (pre) [%]	74.24 ±5.19	72.15±8.76	69.17±8.11	0.192
Lean body mass (post) [kg]	38.24± 7.40	33.41±6.88	36.29±9.15	0.236
Lean body mass (post) [%]	80.63± 5.57	74.61±10.07	68.93±8.98	0.002*
6-minute walk test (pre)	225±72.39	206±69.23	223±76.69	0.729
6-minute walk test (post)	329±70.42	268±65.31	268±79.38	0.033*
Quality of life (pre)	86±20 7	85±20.9	96±14.6	0.199
Quality of life (post)	107±15 89	96±20.32	104±14.58	0.200

The research subjects are 46 NSCLC patients consisting of 15 men and 31 women (*P*=0.990). The average age in the combination group is 60.7±7.43 years, in the creatine monohydrate supplementation-only group is 58.1±8.16 years and in the control group 53.1±14.17 years (*P*=0.135).

Most of subjects 69.5% were having mutation exon 19 with 58.6% received Afatinib, 19.5% received Erlotinib, and 21.7% received Gefitinib (*P*=0.611). With average duration of EGFR TKI therapy was 10.4±9.62 months for first group, 11.06±6.77 months, and 13.27±9.03 months for the second and third group (*P*=0.631). There were 6.5% smokers in first group, 10.9% in second group, and 8.7% in third group (*P*=0.774). The basic characteristics of the research subjects can be seen in Table 1.

The variable analyzed in this study is lean body mass, 6MWT, and quality of life in patients with NSCLC. Lean body mass is assessed in kilograms (kg) and percent (%), a 6-minute walk test is assessed in meters, and quality of life is assessed by a FACT-L questionnaire in the form of total scores. The results of the different tests using one-way ANOVA on each variable showed that lean body mass and 6MWT after treatment had significant differences in all three groups, whereas the other variable showed no statistically significant difference. The characteristics of the variables can be seen in Table 2.

The average value of lean body mass in kg before treatment in the combination group of creatine monohydrate supplementation with upper limb exercise was 34.01±7.16 kg; the creatine monohydrate supplementation group only was 32.23±6.33 kg, and the control group was 36.53±9.55 kg. Lean body mass average score after treatment on the combination of supplementation creatine monohydrate with upper limb exercise group was 38.24±7.40 kg, in the group supplementation creatine monohydrate only was

33.41±6.88 kg; and in the control group was 36.29±9.15 kg. There is significantly increase in lean body mass for first group 4.22±1.81 kg (*P*=0.0001). Second group 1.17±3.45 kg (*P*=0.192) and third group -0.24±1.87 kg (*P*=0.623).

Another assessment for lean body mass (%) was obtained from the total body weight. The average value of lean body mass (%) before treatment in the combination group of creatine monohydrate supplementation with upper limb exercise was 74.24±5.19%; in the supplementation group creatine monohydrate is 72.15±8.76%, and in the control group is 69.17±8.11%.

Table 3. Lean body mass difference pair-test among groups

Groups	Lean body mass			*P*
	Pre	Post	Difference	
Group 1	34.01±7.16 kg	38.24±7.40 kg	4.22±1.81 kg	0.0001*
	74.24±5.19 %	80.63±5.57%	6.38±2.48%	0.0001*
Group 2	32.23±6.33 kg	33.41±6.88 kg	1.17±3.45 kg	0.192
	72.15±8.76%	74.61±10.07%	2.46±7.34%	0.200*
Group 3	36.53±9.55 kg	36.29±9.15 kg	-0.24±1.87 kg	0.623
	69.17±8.11%	68.93±8.98%	-0.23±2.32%	0.699

Table 4. Post hoc test results on changes in lean body mass

Variabel				Mean Difference	*P*
Lean Body Mass (kg)	Bonferroni	Group 1	Group 2	3.057	0.005*
			Group 3	4.494	0.0001*
		Group 2	Group 1	-3.057	0.005*
			Group 3	1.436	0.364
		Group 3	Group 1	-4.494	0.000*
			Group 2	-1.436	0.364
Lean Body Mass (%)	Games-Howell	Group 1	Group 2	3.9220	0.136
			Group 3	6.621	0.0001*
		Group 2	Group 1	-3.9220	0.136
			Group 3	2.699	0.363
		Group 3	Group 1	-6.621	0.0001*
			Group 2	-2.699	0.363

Table 5. Paired test of 6-minute walk test and Quality of Life

Variable		Pre	Post	Diff	*P*
6-minute walk test	Group 1	225±72.39	329±70.42	104±20.07	0.0001
	Group 2	206±69.23	268±65.31	62±28.69	0.0001
	Group 3	223±76.69	268±79.38	45±19.89	0.0001
Quality of life	Group 1	86±20.7	107±15.89	20.80±10.75	0.0001
	Group 2	85±20.9	96±20.32	10.62±7.30	0.0001
	Group 3	96±14.6	104±14.58	7.26±4.81	0.0001

Table 6. Post hoc test results on changes in 6MWT and Quality of life

Variable				Mean Difference	*P*
6MWT	Bonferroni	Group 1	Group 2	42.396	0.0001*
			Group 3	58.533	0.0001*
		Group 2	Group 1	-42.396	0.0001*
			Group 3	16.138	0.185
		Group 3	Group 1	-58.533	0.0001*
			Group 2	-16.138	0.185
Quality of life	Games-Howell	Group 1	Group 2	10.175	0.014*
			Group 3	13.533	0.001*
		Group 2	Group 1	-10.175	0.014*
			Group 3	3.358	0.298
		Group 3	Group 1	-13.533	0.001*
			Group 2	-3.358	0.298

The average value of lean body mass after treatment in the combination group of creatine monohydrate supplementation with upper limb exercise obtained 80.63±5.57%; in the creatine monohydrate supplementation only group it was 74.61±10.07% and in the control group was 68.93±8.98%.

The difference in the addition of lean body mass in the first group was 6.38±2.48% (*P*=0.0001), 2.46±7.34% (*P*=0.200), and there is the decrease of lean body mass on group control -0.23±2.32% (*P*=0.699). The differences can be seen in Table 3.

The multivariate test showed *P*<0.05 means there was a significant difference between the three groups. The homogeneity test on lean body mass in kg (*P*=0.084), which means the data was homogeneous, so it continued with the post hoc Bonferroni test. The post hoc test results for lean body mass (kg) stated that the combination of creatine monohydrate supplementation with upper limb exercise was significantly different compared to the creatine monohydrate supplementation group and the control group.

Lean body mass in percentage data was homogenous (*P*=0.01), so analyzing continued with the Games-Howell post hoc test. The post hoc test results stated that the combination of creatine monohydrate supplementation with upper limb exercise was not significantly different compared to the creatine monohydrate supplementation group only but significantly different from the control.

The average value of the 6MWT before treatment in the combined creatine monohydrate supplementation group with upper limb exercise was 225±72.39 meters, in the creatine monohydrate supplementation group, only 206±69.23 meters, and in group control is 223±76.69 meters. The average value of the 6-minute walk test after treatment in the combination group of creatine monohydrate supplementation with upper limb exercise was 329±70.42 meters, in the creatine monohydrate supplementation group only was 268±65.31 meters, and in the control group is 268±79.38 meters. The increase of the 6-minute walk test in the combination group of creatine monohydrate supplementation with upper limb exercise, creatine monohydrate supplementation-only group, and control is 104±20.07 meters *P*=0.0001), 62±28.69 meters (*P*=0.0001), and 45±19.89 meters (*P*=0.0001) respectively.

The mean score of the quality of life before treatment in the combination group of creatine monohydrate supplementation with upper limb exercise obtained 86±20.7; in the creatine monohydrate supplementation group only was 85±20.9, and in the control group was 96±14.6. The average value of quality of life after treatment in the combination group of creatine monohydrate supplementation with upper limb exercise was 107±15.89; in the creatine monohydrate supplementation-only group was 96±20.32, and in the group control was 104±14.58. The difference in the addition of quality of life in the combination group of creatine monohydrate supplementation with upper limb exercise, creatine monohydrate supplementation-only group, and control group each 20.80±10.75; 10.62±7.30; and 7.26±4.81 respectively in the three groups *P*=0.0001, which mean that there was a statistically significant change in the quality of life score.

Both of 6-minute walk test and quality of life have larger additions in the combination of creatine monohydrate supplementation with the upper limb exercise group compared to the creatine monohydrate supplementation-only group, and the control group. The change is statistically significant if *P*<0.05 occurred in the three groups. The differences can be seen in Table 5.

The statistical test for changes in the 6MWT and quality of life score was followed by the Kolmogorov-Smirnov test and continued with the homogeneity test. The homogeneity test on the 6MWT was found *P*=0.173, means that the data was homogeneous. The value of quality of life *P*=0.01, means that the data was not homogeneous. Both data followed by a multivariate test showed the value of *P*<0.05 meaning there was a significant difference in the three groups and followed by a post hoc test Bonferroni for the 6MWT and Games-Howell for quality of life.

The post hoc test results stated that the combination of creatine monohydrate supplementation with upper limb exercise was significantly different compared to the creatine monohydrate supplementation group and the control group. The creatine monohydrate supplementation group only was not significantly different from the control group. It means combination groups have a superior effect on the 6MWT and quality of life. The results can be seen in Table 6.

DISCUSSION

This research is a quasi-experimental study to determine the effect of the combination of creatine monohydrate supplementation and upper limb exercise on muscle dysfunction and quality of life in patients with NSCLC. Muscle dysfunction assessment covers lean body mass and a 6MWT. NSCLC patients that met the inclusion criteria from September–November 2020 count 49 subjects. There were 3 subjects discontinued the study post-treatment because of passed away and statistical analysis was carried out on 46 research subjects which 2 subjects from the first group and 1 subject from the third group.

The research subjects were 46 subjects with NSCLC consisting of 32.6% males and 67.4% females. These data are similar to several studies including studies by Zhang in the year 2016 stated that EGFR mutation is higher in a woman 43.7% compared to men 24%.[20] Average age of subjects in creatine monohydrate supplementation combined with upper limb exercise group was 60.7±7.43 years, the creatine monohydrate supplementation-only group was 58.1±8.16 and in the control group 53.1±14.17. A study by Devi in 2021 showed that NSCLC patients at dr. Moewardi is mostly 60-70 years.[21]

There are 26.1% subjects who have a smoking history and 73.9% subjects have no smoking history. Other criteria with exon 19 mutation happened in 69.6%. These data are similar to the study by Zhang (2016) which patients with NSCLC without a smoking history were 49.3% compared to those with no smoking history by 21.5%. Most of the research subjects with exon 19 mutations were 75.21%.[20]

The study by Hsu et al (2018) reported that EGFR mutations occur at some point between exons 18 and 21. Exon 19 deletions and mutations point L858R on exon 21 is a generally detected type mutation and accounted for 50% and 40% of all patients, respectively. The two types of mutations are sensitization mutations and tumors with these mutations are sensitive to EGFR tyrosine kinase inhibitors (TKI).[3]

The average value of initial lean body mass in the first group was 34.01±7.16 kg and 74.24±5.19 %, respectively. The average initial lean body mass in the second group was 32.23±6.33 kg and 72.15±8.76%, and in the third group was 36.53±9.55 kg and 69.17±8.11 %, respectively. The increasing of lean body mass in the first group of was 4.22±1.81 and 6.38±2.4 %, (P=0.0001) greater and statistically significant.

A study by Xiao et al in 2017, based on the National data Health and Nutrition Examination Survey (NHANES) III obtained the median value of percetage body fat is 24% in men and 40% in women aged less than 40 years with body mass index normal, as well as 28% for men and 45% for women aged >70 years. The normal value for lean body mass is 70–90% of total body weight.[22] Increasing of lean body mass on the first group and second group showed a normal value so that supplementation with creatine monohydrate can help improve lean body mass clinically assisted by a combination of upper limb exercise so that the addition of lean body mass increased.

The research data according to a study by Olsen in 2006 reported that in healthy humans, creatine monohydrate supplementation in combination with progressive resistance training (PRT) strengthened the increase in satellite myocytes and concentration of myonuclei in skeletal muscle fibers, thereby facilitating muscle growth and hypertrophy.[23] Other studies by Sakkas in 2009 demonstrated that creatine monohydrate supplementation augmented the effects of PRT on muscle strength, energy, and body composition in 27 immunocompromised patients.[24]

Studies related to supplementation of creatine monohydrate by Jatoi (2017) failed to show the benefit which can be demonstrated in lean body mass, muscle strength or function. Inactive muscle conditions can cause decreased absorption of creatine monohydrate thereby interfering with the effects of creatine supplementation on lean body mass and muscle strength.[25]

The average of initial 6MWT in the first group obtained 225±72.39, 206±69.23 for second group, and in the third group was 223±76.69 (*P*=0.729) after the one-way ANOVA test showed no significant difference between groups. The average value of the 6MWT after treatment in the first group was 329±70.42, 268±65.31 for second group and 268±79.38 in third group (*P*=0.033) after one-way ANOVA test showed there was difference mean among groups. The difference in the addition of a 6MWT in the first, second, and third group each 104±20.07, 62±28.69, and 45±19.89 respectively with each group conducted paired t-test and obtained *P*=0.0001 indicates there is a significant change.

The measurement of the 6MWT was carried out by the recommendations of the American thoracic society in 2002 as a measure of response to therapeutic interventions for cardiorespiratory disease.[9] The research data is similar to a study by Peddle-McIntyre in 2019 stated that patients who exercised a 6MWT were 63 meters higher than 122 meters.[6] Another study by Edbrooke 2019 showed a change in the 6MWT after the first 8 weeks of the intervention there was a difference between the control and intervention groups of 48 m.[19]

The average value of initial quality of life in the first group was 86±20.7, 85±20.9 for second group and in the third group was 96±14.6. all three groups showed no significant difference *P*=0.199. The average quality of life after treatment in the first group of was 107±15.89, in the second group was 96±20.32 and in the third group was 104±14.58 (*P*=0.2).

The different quality of life in were 20.8±10.75; 10.62±7.30; and 7.26±4.81 (*P*=0.0001) each group respectively. The data was similar to a study by Peddle-McIntyre in 2019 that reported that exercise in advanced lung cancer patients increased health-related quality of life (HRQoL) by 13.0 (*P*=0.005).[6] Another study by Gerritsen in 2016 reported that exercise intervention improved the quality of life in cancer patients significantly by 5.55 (SD=3.19-7.90) with *P*<0.001.[26]

Research data in the form of changes in lean body mass, 6MWT, and quality of life in the combination group of creatine monohydrate supplementation and upper limb exercise as first group, creatine monohydrate supplementation-only as second group, and the third group were tested for normality with the Kolmogorov-Smirnov test, and obtained lean data body mass and 6MWT distributed normally each value of *P*=0.2 and *P*=0.071 while the quality of life was not normally distributed (*P*=0.0001). The homogeneity test showed that the lean body mass and 6-minute walk test data were homogeneous with value of *P*=0.084 and *P*=0.173, respectively. Quality of life data in the study showed that the data was not homogeneous with value of *P*=0.001. Homogeneity test affected post hoc test after one-way test ANOVA.[24,25]

The study of Roger Harris (1992) showed that oral creatine intake can increase intramuscular creatine content to increase exercise capacity.[16] Study by Buford (2007) reported that creatine as supplement nutrition is most effective to increase exercise tolerance, muscle strength, and LBM.[27] Study by Greenhalf (1995) reported that consumption of creatine 20 grams/day for 5 days can increase more than 20% of muscle creatine in the form of PCr.17 Study by Hultman (1996) used tissue biopsy to determine total muscle creatine levels show that there was a decrease in total creatine levels of 6 mmol/kg dm at 14 days after creatine monohydrate supplementation was discontinued.[28]

Cr supplementation in patients with muscle inactivation did not show the expected effect. Olsen

(2006) reported that in healthy people, Cr supplementation in combination with progressive resistance training (PRT) strengthened the increasing number of satellite cells and concentration of myonuclei in skeletal muscle fibers, thereby facilitating muscle growth and hypertrophy.[23] Creatine monohydrate has also been shown to increase the expression of myogenin and other myogenic regulatory factors that regulate the expression of the myosin heavy chain, which affects the content of contractile proteins like actin and myosin.[13,14,29]

Lean body mass, 6-minute walk test, and quality of life of research subjects showed significant numbers after the one-way ANOVA test with value of *P*=0.0001 at that three variables. Post hoc test on the lean body mass and 6-minute walk test data using Bonferroni. The results of the Bonferroni test on lean body mass data showed significantly different results between the combination group of creatine monohydrate supplementation with upper limb exercise, compared to the creatine monohydrate supplementation-only group (*P*=0.005) and the control group (*P*=0.0001). There was no significant difference between the creatine monohydrate supplementation-only group with the control group (*P*=0.364).[24,25]

Bonferroni test results on 6-minute walk test data obtained different means between a combination of creatine monohydrate supplementation with upper limb exercise group, compared to the creatine monohydrate supplementation-only group (*P*=0.0001) and the control group (*P*=0.0001). There was no significant difference between the creatine monohydrate supplementation group and the control group (*P*=0.185).[24,25]

Post hoc test on the quality of life data used the Games-Howell test and obtained significantly different results among the combination of creatine monohydrate supplementation with the upper limb exercise group, compared with the creatine monohydrate supplementation-only group (*P*=0.014) and with the control group (*P*=0.001). There was no significant difference between the creatine monohydrate supplementation group and the control group (*P*=0.298). The results were consistent with a study by Sakkas (2009) showed that supplementation of creatine monohydrate augmented the effects of PRT on muscle strength, energy, and body composition in 27 immunocompromised patients, and the Jatoi study (2017) that supplementation with creatine monohydrate only failed to show any demonstrable benefit in lean body mass, strength or muscle function.[24,25]

LIMITATIONS

A limitation of this study is the possibility of data bias. Treatment in the form of supplementation and home-based exercise requires cooperation with the patient's family and regular monitoring. The patient's family cannot always be contacted for telemedicine. The assessment of the 6-minutes walking test criteria after treatment was influenced by the results of the initial assessment.

CONCLUSION

Creatine monohydrate supplementation and upper limb exercise affect the lean body mass, 6-minute walk test, and quality of life in NSCLC patients. A combination of creatine monohydrate supplementation and upper limb exercise has superior effects compared to creatine monohydrate only and control.

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CONFLICT OF INTEREST

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