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Original Article

Impact of preoperative pulmonary rehabilitation on postoperative outcomes in patients undergoing lung cancer surgery

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ABSTRACT

Background: In this study, it was planned to improve the respiratory and metabolic capacities of patients who will be operated for lung cancer in the preoperative period. Thus, the effect of preoperative pulmonary rehabilitation (PPR) on postoperative morbidity / mortality rates and the duration of hospital stay was investigated.

Materials and Methods: Between July 2020 and February 2021, 43 patients who were operated for lung cancer were evaluated prospectively. Group I (n = 20) patients were included in the PPR program for 2 weeks preoperatively. PPR was not applied to the control group, Group II (n = 23) patients. Demographic findings of the cases, postoperative length of stay and drain duration, postoperative complication development were compared.

Results: The mean age of Group I was 63.60 ± 5.87 (54-75), while that of Group II was 60.78 ± 13.30 (32-83). Surgical mortality was not observed in any patient. While morbidity was observed in 7 (35%) patients in Group I and 13 (65%) patients in Group II ($p = 0.158$). The postoperative hospital stay of Group I was found to be statistically significantly lower than Group II ($p = 0.026$). It was determined that the drain stay time of Group I patients was shorter than Group II ($p = 0.009$).

Conclusion: It was seen that the importance of preoperative pulmonary rehabilitation was high in achieving less complications and shorter hospital stay in the postoperative period in patients who underwent pulmonary rehabilitation due to lung cancer surgery.

Keywords: lung surgery, non-small cell lung cancer, pulmonary rehabilitation, morbidity

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Introduction

Lung cancer is the second most common type of malignancy worldwide and one of the leading causes of cancer-related mortality. Lung cancer creates an important burden of disease on society and the economy is seriously affected by this burden [1]. Surgical resection, because of its chance of curability, has higher survival rates compared to all other treatment methods. However, it can be related to significant morbidity, functional losses and a decrease in the quality of life [2,3]. Despite the preoperative examinations, complications may occur during the postoperative period, hence the length of hospitalization may be prolonged. For this reason, studies on this subject suggest that preoperative pulmonary rehabilitation (PPR) programs together with exercise, can improve the exercise capacity, functional performance, and quality of life, both before and after the operation [2-5]. PPR is a comprehensive intervention that includes, exercise training (durability and resistance) and behavioral changes for the patient [6,7]. It is known that patients with low exercise tolerance have worse outcomes of thoracic surgery morbidity/mortality compared to other patient groups [8]. Therefore, it is hoped that PPR can decrease postoperative complications and morbidity, shorten the length of hospitalization, and reduce healthcare costs [8].

This study aimed to show the increase the metabolic and respiratory capacities of patients in the preoperative period with PPR, thus it is planned to increase the tolerability of surgical procedures, having less complications in the postoperative period and shorter length of hospital stay.

Materials and Methods

Between the dates of July 2020 and February 2021, patients who were operated on because of non-small cell lung cancer (NSCLC) were included in the evaluation. Randomization is achieved by coin flipping between the eligible patients who applied to the outpatient clinic to be included in the study and control groups. The patients who cannot do physical exercise due to comorbidity, who will be operated on because of benign pathology or metastatic lung disease, who have a history of cardiac operation and also patients with history of orthopedic operation with a prosthesis, and recent history of major surgery because of other reasons are excluded in the study. Patients who completed a PPR program that matches the criteria are included in the study.

All patients included in the study completed their preoperative diagnostic and evaluation procedures at

the Ege University Faculty of Medicine, and the surgical interventions were likewise performed in the same institution, ensuring consistency in preoperative assessment, perioperative management, and postoperative follow-up within a standardized institutional setting.

Group I patients, which is the study group, were additionally included in a pulmonary rehabilitation program, before the operation for 2 weeks. The method of randomization was based on selecting individuals who, within the study period, had no contraindications for the Pulmonary Rehabilitation (PR) program and expressed willingness to participate. Group II patients, which is the control group, were operated on without any additional application, with routine preoperative preparations. 20 patients for Group I, 23 patients for Group II were included in this prospective study. The age, sex, comorbidity, technique of surgical procedure, figures of forced expiratory volume in one second (FEV1) before the pulmonary rehabilitation (PR), figures of arterial blood gases before the PR, postoperative length of hospitalization, surgical diagnosis, postoperative complications, the length of tube thoracostomy treatment, smoking history and postoperative early period mortality of total 43 patients were researched.

Patients of both groups were evaluated by the blood biochemistry, electrocardiogram (ECG), respiratory function test, posteroanterior and lateral chest x-ray, thorax CT. When required, PET/CT and MRI evaluations were done. For the diagnosis, one or more of following techniques were used; sputum cytology, transthoracic fine-needle aspiration biopsy (TTFNAB), evaluation with bronchoscopy (lavage, bronchial brushing, biopsy). The staging of the cases were done according to the 'International Association for the Study of Lung Cancer (IASLC)'s 2017 international lung cancer classification. Histopathologic typing was determined according to World Health Organisation's 2015 classification.

In scope of the study, 20 patients that were willing to participate in the program and who did not have any contraindications for pulmonary rehabilitation, were subjected to bronchial hygiene methods, exercise techniques (respiratory, aerobic, stretching, and relaxation exercises) and information that could be applied to the daily life were given one time during the program. At the preoperative period, the Group I cases were included in a pulmonary rehabilitation program that consisted exercises of joint range, aerobic (walking and spinning), strengthening (forced stretching movements, weight training, etc.), re-

spiratory (forced inhalation and exhalation that strengthens the respiratory muscles), relaxation and stretching to be practiced by the physicians, physiotherapists, and technicians who were trained about this subject and all rehab program to be completed at the pulmonary rehabilitation unit for 2 weeks, 5 days a week, 1.5 hours in a day. Cases were also asked to do an exercise program once a week at home. Joint range exercise consisted of 10 rep of neck, waist, upper, and lower body extremities joint exercises which were done before the aerobic exercise. Aerobic exercise was done for 30 minutes total, 15 minutes treadmill, and 15 minutes spinning. It was performed to reach 60-70% of VO₂max and 60-70% of heart rate reserve, as moderate-intensity exercise. 23 cases in Group II, did not have any rehabilitation before the operation and these cases formed the control group.

Complications were classified as prolonged air leak, subcutaneous emphysema, pneumonia, atelectasis requiring bronchoscopy, postoperative expansion defect, pulmonary embolism, blood product transfusion, intraoperative bleeding, postoperative hemorrhage, arrhythmia, and metabolic disorder.

The ethical approval for this study was obtained from the Ethics Committee of Medical Research at Ege University in 06/2020 (Approval No: 20-6T/50).

Statistical Analysis

Statistical analyses were done by using the "Statistical Package for Social Sciences (SPSS) " 24.0 program. Categorical data was stated as numbers and percentages. Numerical data was stated as average \pm standard deviation and normal (minimum-maximum). The normality control of the numerical variables in the groups was done with the "Shapiro-Wilk test". For the comparison of numerical variables in groups, "The Independent t-test and Mann-Whitney U test" were used. "The K-square test" was used for the comparison of categorical variables in groups. A p-value less than 0.05 was defined as statistical significance.

Results

The mean age of Group I (study group) was 63.60 ± 5.87 (54-75) and the number of female patients' were 4 (20%). Right upper lobectomy was performed on 5 patients, right lower lobectomy on 4 patients, segmentectomy on 3 patients, middle lobectomy on 2 patients, left upper lobectomy on 2 patients, left lower lobectomy on 2 patients, left pneumonectomy on 1 patient, and wedge resection on 1 patient. While 5 (25%) of these procedures were performed videothoraco-

scopically, 15 (75%) patients underwent lateral thoracotomy. It was detected that 11 (55%) of the patients were diagnosed with squamous cell carcinoma, 8 (%40) with adenocarcinoma, 1 (5%) with adenosquamous carcinoma. 16 (80%) of the patients had co-morbid illnesses. 9 (45%) of the patients did not have a history of smoking (Table 1). While no mortality was observed on any patient in the post-operation early period, one of the patients underwent revision due to hemorrhage. Morbidity (prolonged air drainage on 5 patients, increased urea-creatinine levels on 1 patient, and hemorrhage on 1 patient) was detected on 7 (35%) patients.

The mean age of Group II (control group) was 60.78 ± 13.30 (32-83) and the group consisted of 18 (78%) male, 5 (22%) female patients. Right upper lobectomy was performed on 7 patients, left upper lobectomy on 6 patients, left lower lobectomy on 4 patients, right lower lobectomy on 3 patients, middle lobectomy on 1 patient, superior bilobectomy on 1 patient, and left pneumonectomy on 1 patient. While 3 (13%) of these procedures were performed videothoracoscopically, 20 (87%) patients underwent lateral thoracotomy. Nine (%39) of the patients got diagnosed with squamous cell carcinoma, 8 (%35) with adenocarcinoma, 3 (13%) with an atypical carcinoid tumor, and 1 each (4.3%) with large cell neuroendocrine carcinoma, lymphoepithelioma-like carcinoma, and large cell carcinoma. Fifteen (65%) of the patients had co-morbid illnesses. Seven (65%) of the patients in Group II did not have a history of smoking. In the early post-operative period, while no mortality was observed on any patient, morbidity (prolonged air drainage in 10 patients, increased urea-creatinine levels in 1 patient, pulmonary embolism in 1 patient, pneumonia in 1 patient, subcutaneous emphysema in 1 patient and sinus bradycardia in 1 patient) were detected in 13 (65%) patients. In the evaluation of normality of numerical variables between groups, age, preoperative values of FEV1 "liter" and "%", preoperative values of PO₂ and PCO₂ in arterial blood gases did demonstrate a similar distribution between groups (Table 2).

In the pre-PR measurements of cases, Group I's average FEV1 ml and % values were 2340 ± 691 (760-3630) ml and 82.2 ± 21.2 % (40-114), Group II's 2648 ± 763 (1230-4130) ml and 92.3 ± 16.8 % (52-117) as resulted in (for ml p = 0.176, for % p = 0.088) (Table 2).

According to pre-PR arterial blood gases measurement results, Group I's cases average PaO₂ (mmHg) value was 87.8 ± 12.8 (59-110), PaCO₂ value was 37.5 ± 4.8 (28.4-47.5) and oxygen saturation value was 97.6

(92-99). In Group II's cases the average PaO_2 (mmHg) value was 97.7 ± 23 (60-166), PaCO_2 value was 37.4 ± 3.8 (31.1-47.1), and oxygen saturation value was 98.1 (93.9-99.7). There was no statistical difference between the two groups (p ; 0.096, 0.990, 0.122) (Table 2).

When we evaluate the post-operative hospitalization length of stay, while Group I's results were average 5.6 ± 1.8 (2-9)/day, Group II's results were found to be 8.35 ± 5.76 (3-27)/day. When comparing groups, there was a statistically significant difference between them ($p = 0.026$) (Figure 1) (Table 3).

The length of tube thoracostomy treatment in the post-operative period was compared. While Group I's results were average 5 ± 3.5 (2-18)/day, Group II's results were 8.7 ± 5.9 (3-24)/day. The difference between groups was statistically significant ($p = 0.009$) (Figure 2) (Table 3).

When the complication development status in the postoperative early period was evaluated, 7 (35%) cases in Group I and 13 (56.5%) cases in Group II postoperative morbidity were detected. Although there was a difference between groups, the difference was not statistically significant. ($p = 0.158$) (Table 4).

Table 1. Demographic and clinical characteristics.

	Group I (N=20)	Group II (N=23)	P-value
Gender			0.889
Female	4 (20%)	5 (22%)	
Male	16 (80%)	18 (78%)	
Age (avg., range, year)	63.6 (54-75)	60.8 (32-83)	0.366
Comorbidity			0.281
Present	16 (80%)	15 (65%)	
Absent	4 (20%)	8 (35%)	
Surgical technique			0.315
Thoracotomy	15 (75%)	20 (87%)	
VATS	5 (25%)	3 (13%)	
Histopathological diagnosis			0.167
Adenocarcinoma	8 (40%)	8 (35%)	
Squamous cell carcinoma	11 (55%)	9 (39%)	
Other	1 (5%)	6 (26%)	
Smoking			0.053
Present	11 (55%)	6 (35%)	
Absent	9 (45%)	17 (65%)	

Abbrev.: VATS: video-assisted thoracic surgery; Avg.: Average.

Table 2. Preoperative respiratory function parameters.

	Grup I (N=20) Avg. (interval)	Grup II (N=23) Avg. (interval)	P-value
FEV1 (L) [before PR]	2.3 (0.76-3.6)	2.6 (1.2-4.1)	0.176
FEV1 % [before PR]	82.2 (40-114)	92.4 (52-117)	0.088
Preop. PaO_2 (mmHg)	87.8 (59-110)	97.7 (61-166)	0.096
Preop. PaCO_2 (mmHg)	37.5 (28-47)	37.4 (31-47)	0.990
Preop. saturation	97.6 (92-99)	98.1 (93.9-99.7)	0.122

Abbrev.: FEV1 : forced expiratory volume in one second, L : liter, PR : pulmonary rehabilitation, Preop: preoperative, Avg. : Average

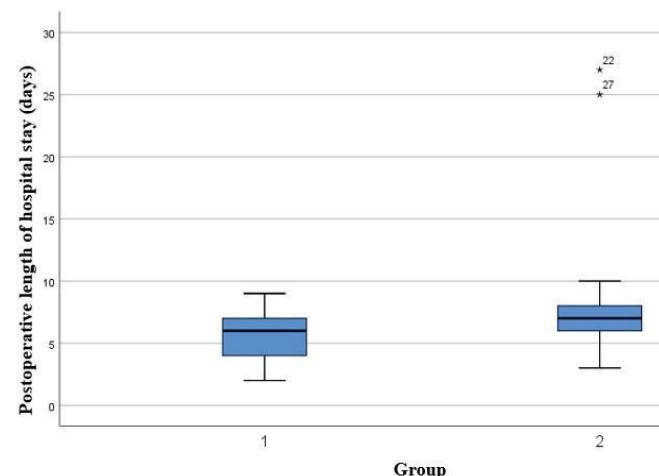


Figure 1. Postoperative length of hospital stay.

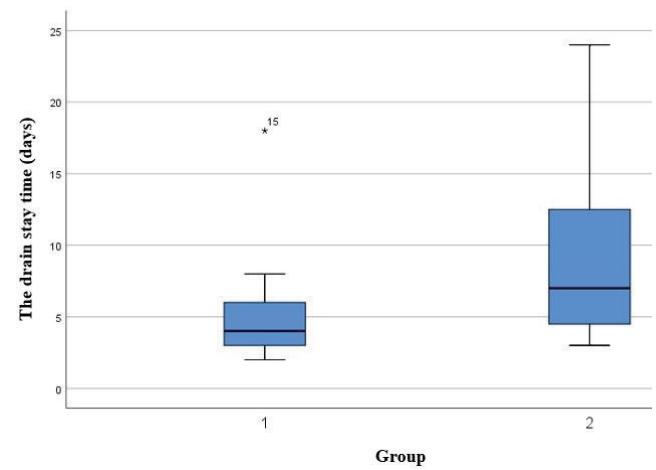


Figure 2. Duration of chest tube drainage.

Table 3. Comparison of postoperative hospitalization and tube thoracostomy duration.

	Grup	n	Average	Standard deviation	Min.	Max.	P value
Postoperative duration of hospitalization (day)	I	20	5.60	1.88	2	9	0.026
	II	23	8.35	5.77	3	27	
	Total	43	7.07	4.57	2	27	
Postoperative duration of tube thoracostomy (day)	I	20	5.00	3.54	2	18	0.009
	II	23	8.70	5.99	3	24	
	Total	43	6.98	5.29	2	24	

Table 4. Distribution of postoperative mortality-morbidity-revision according to the groups.

Grup	Postoperative morbidity		Total	P value
	Present	Absent		
I (n, %)	7, 35%	13, 65%	20, 100%	0.158
II (n, %)	13, 56.5%	10, 43.5%	23, 100%	
Total	20, 46.5%	23, 53.5%	43, 100%	
Grup	Revision		Total	P value
	Present	Not present		
I (n, %)	1, 5%	19, 95%	20, 100%	0.278
II (n, %)	0, 0%	23, 100%	23, 100%	
Total	1, 2.3%	42, 97.7%	43, 100%	
Grup	Mortality (first 1 month)		Total	P value
	Present	Not present		
I (n, %)	0, 0%	20, 100%	20, 100%	
II (n, %)	0, 0%	23, 100%	23, 100%	
Total	0, 0%	43, 100%	43, 100%	

Discussion

It is predicted that the number of patients who will be operated on for early-stage lung cancer will increase with the improvement in lung cancer awareness and developments in imaging methods in recent years. Postoperative complication and mortality risk after lung resection represent significant limitation for surgical treatment of lung cancer. For this reason, there can be potential of decreasing the postoperative risk and hospitalization length by managing the modifiable risk factors, at the same time, it is hoped that it will have a positive effect on health care costs [9]. Many studies in the literature indicate that the practice of pulmonary rehabilitation decreases postoperative morbidity in colorectal, heart, and spinal surgeries [10]. The results of these studies, collected under the name of ERAS: Enhanced Recovery After Surgery, in the specialty fields like colorectal surgery and examined in detail. In the aim of accelerating

the recovery, it is planned to restore the postoperative organ dysfunction. With the practice of many evidence-based preoperative measures, serious results have been achieved. In conclusion, the information of decrease in the hospitalization lengths and postoperative complication rates were attained [11]. In general, ERAS interventions in thoracic surgery are divided into preoperative, intraoperative, and postoperative periods. In the preoperative period, nutritional evaluation and support, correction of the anemia and smoking cessation are the leading factors. The intraoperative period focused on minimally invasive surgery (VATS) with optimal analgesic technique, when possible. In the postoperative period, the main goals are the management of pain, early mobilization, early oral intake, and prevention of nausea and vomiting. However, it has been stated that improvement of patients' pulmonary function and exercise capacity may reduce the risk of complication [12].

In the light of all these examples and suggestions, it is encouraging to research the role of PPR in the patients who will undergo pulmonary resection. The hypothesis regarding the effect of PPR is such that, if the existing respiratory functions of the patients are improved in the preoperative evaluation, postoperative complications and mortality can be reduced. In this prospective study, we researched the PPR's effect on the tolerability of surgery, postoperative morbidity/mortality ratio and hospitalization length by planning to improve preoperative respiratory and metabolic capacities of the patients who will be operated on due to lung cancer. Although there is no consensus on the duration of preoperative pulmonary rehabilitation in many studies based on this hypothesis in the literature, the durations have been found to range from one day to four weeks before the operation [13]. Divisi et al [14] observed a monotypic group of 27 patients with a diagnosis of COPD and NSCLC in their studies and performed lobectomy after subjecting all the patients to a 4 week of PPR program. Likewise, Sekine et al [15] evaluate the effect of a 2-week program of PPR on patients who underwent a lobectomy and showed that PPR decreases the length of hospitalization. In a study, Yanez-Brage et al [16] evaluated the postoperative pulmonary complications in patients who underwent coronary artery bypass graft surgery. It has been stated that 1 day of preoperative physiotherapy can significantly reduce the atelectasis. Hulzebos et al [17] applied 2 weeks of inspiratory muscle exercises to the 140 patients out of 279 who underwent elective coronary artery bypass graft surgery and show that postoperative pulmonary complications were significantly reduced. In the light of these examples in literature, we planned a 2 week of pulmonary rehabilitation program similar to previous studies, considering the oncological waiting times.

The studies have shown that PPR is safe for resectable lung cancer patients, improves the results of respiratory function test and cardiopulmonary exercise test [18]. However, these development's effect on postoperative complications and mortality has not been clear. It was thought that reasons such as clinical trials have failed to show the statistically significant difference, not randomizing, patient selection or short-term PPR practice reveal these results. The low number of patients included in the study and other limitations prevent the generalization of results.

In the study done by Benzo et al [19], it is shown that randomly selected patients with the diagnosis of COPD and NSCLC, for the preoperative exercise therapy program who underwent lung resection, had a shorter duration of postoperative tube thoracostomy treatment (4.3 days in comparing to 8.8 in the control group, $p = 0.04$) and also it is shown the incidence of long duration of tube thoracostomy (>7 days) is lower (11% against 63%, $p = 0.03$) comparing to the control group. In addition, the patients in the preoperative exercise therapy arm of the study were found to have shorter hospital stays which was almost significant. For the postoperative pulmonary complication incidence, no significant difference (patients who need bronchoscopy due to respiratory failure, pneumonia, atelectasis, $p = 0.45$ (for every 3 outcome criteria)) was found [19].

The study carried by Bobbie et al [20], includes 11 cases (monotypic group) operated on between 2004-2006 due to NSCLC and underwent 4 weeks of preoperative pulmonary rehabilitation. Although the study has found that significantly meaningful improvement of 2.8mL/kg/min at VO2max values and is one of the first studies that practiced PPR. It was insufficient to produce meaningful results due to the lack of a control group.

Morano et al [20] have reported that the patients who are in the preoperative exercise program have spent fewer days (7.8 ± 4.8 against 12.2 ± 3.6 days, $p = 0.04$) at the hospital (comparing to the control group), keeping the chest tube fewer days (4.5 ± 2.9 against 7.4 ± 2.6 days, $p = 0.03$) and lower incidence of postoperative pulmonary complications (16.7% against 77.8%, $p = 0.01$).

The case-control study done by Varela et al [21] has emphasized that the mortality in the preoperative exercise group was lower compared to the control group. It was reported that the rates of pneumonia and atelectasis were found to be higher in the control group, but only the difference in atelectasis rates was significant. The mean hospital length of stay was found to be significantly less in the preoperative exercise therapy group.

Gao et al [22] published a study of 142 high-risk patients with potentially resectable lung cancer in 2015. The patients were non-randomly allocated to the study group (71 patients) who underwent a preoperative pulmonary rehabilitation program followed by lobectomy, and to

the control group who underwent only lobectomy with conventional treatment, and the postoperative complication rate in the study group was found to be significantly lower than in the control group. While the postoperative hospital length of stay was significantly longer in the control group, there was no difference between the two groups in terms of the analysis of the average cost in the hospital, including the cost of pulmonary rehabilitation.

In a randomized clinical trial conducted by Licker et al [18] in 2017; 25-day PPR was applied to 74 out of 151 lung cancer patients who were to undergo elective surgery and the results compared with the control group of 77 cases. When the VO₂max and six-minute walk test results were compared between the two groups, in the PPR group; a statistically significant 15% increase was found for both values. An 8% decrease in VO₂max was observed in the control group, and there was no statistical difference in postoperative complications (or hospital stay) between the groups.

In our prospective study researching the effectiveness of the pulmonary rehabilitation (PR) program applied for 2 weeks before the operation in patients with NSCLC who were planned pulmonary resection, it was shown that PPR caused a statistically significant decrease in postoperative hospitalization time and chest tube treatment time ($p < 0.05$).

Limitations of the study

There are several limitations of our study that should be considered when evaluating the results. One of these limitations is, we had to carry out this prospective study during the Covid-19 pandemic, which resulted with lower number of cases. Although there were fewer complications in the PPR group, no statistically significant difference was observed, possibly due to limited number of cases. As we mentioned before, the effect of PPR on postoperative complications and mortality could not be found to be statistically significant in many studies, similar to our study in the literature [18,19,21]. Another limitation was that the VATS procedure alone can reduce postoperative pulmonary complications and mean hospital stay, and thus affecting the outcomes. It is thought that the interaction between VATS/thoracotomy surgical procedure type and pulmonary rehabilitation should be investigated with a further study. Our results require confirmation with a larger and possibly multicenter study.

In conclusion, our findings suggest, short-term pulmonary rehabilitation has positive effects on pulmonary functions, inspiratory muscle strength, exercise capacity, and dyspnea in patients with lung cancer. We think, the positive effects of preoperative pulmonary rehabilitation emerged objectively in our study. We see this rehabilitation program as effective management of pulmonary rehabilitation in the perioperative period in our cases, in which we observed significant improvement of lung function, exercise capacity and quality of life.

Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

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Ethics approval

The ethical approval for this study was obtained from the Ege University Ethics Committee of Medical Research at 06/2020 (Approval No: 20-6T/50).

Authors' contribution

MEU: Definition of intellectual content, Statistical analysis, Manuscript preparation. TİA: Design, Definition of intellectual content. FEU: Clinical Studies. AGE: Data acquisition. AÖ: Literature Search, Review. KT: Literature Search, Review. AG: Clinical Studies. MÜ: Definition of intellectual content, Statistical analysis, Manuscript preparation. AC: Editing, Review. UC: Editing, Review.

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