Study of Insomnia in Chronic Obstructive Pulmonary Disease Patients at a Tertiary Care Centre

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Abstract

Background: Chronic Obstructive Pulmonary Disease (COPD) is a common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities caused by significant exposure to noxious particles or gases. Aims and Objectives: 1. To estimate the proportion of insomnia in Chronic Obstructive Pulmonary Diseases patients, 2. To study the association of insomnia with severity of Chronic Obstructive Pulmonary Diseases among study participants and 3. Assessment of Quality of Life among study participants. Materials and Methods: This prospective observational study was conducted in Department of Respiratory Medicine in a tertiary care center and medical college. Written informed consent was taken from all the study participants and those who gave consent were enrolled in the present study. Total 159 COPD patients were included in the study, after satisfying the eligibility criteria. The COPD patients were enrolled after satisfying the eligibility criteria given GSAQ Questionnaire to find the presence of insomnia, PSQI for quality of sleep and then SF-36 score questionnaire to assess Quality of Life. Study was conducted for duration of 2 years (August 2018 to December 2020). Observation and Results: The most common age group amongst study population was 51 to 60 years (42%) followed by 40 to 50 years (29%) and more than 60 years (29%). There was male predominance (54.5%) in the study population as compared to females (45.5%). The most common occupation amongst study population was farmer (28%) followed by Shopkeeper (23%) and Driver (19%) and most of the study population were obese (65.2%) followed by normal BMI (28.8%) and underweight (6.1%). Most of the study population were Grade 2 dyspnea (36%) followed by Grade 3 (34%) and Grade 4 (16%). Most of the study population were Moderate COPD (45.5%) followed by severe COPD (27.3%) and very severe (21.2%). Comorbidities like Diabetes and Hypertension was observed in 11% and 28% of study population. 29% of study population was ex smokers. 69.57% of ex smokers had more than 20 pack years while 30.43% had less than 20 pack years. The prevalence of insomnia in our study population was 43%. The prevalence of insomnia was most commonly observed in severe COPD (40%) followed by Very severe COPD (35%), Moderate COPD (19%) and mild COPD (6%) and the difference was statistically significant. Mean Physical health score and Mental health score was significantly higher in insomniac patients as compared to non insomnia patients. Mean PSQI was significantly higher in insomniac patients as compared to non insomnia patients. Conclusion: 40% of our patients with COPD experienced poor sleep quality. Presence of insomnia in patients with COPD is also associated with increased day time sleepiness and worse QOL.

Keywords: COPD - Chronic Obstructive Pulmonary Disease, GSAQ - Global Sleep Assessment Questionnaire, PSQI – Pittsburgh Sleep Quality Index, SF 36 - Short form 36 Health Survey Questionnaire

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1. Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities caused by significant exposure to noxious particles or gases.

The major and significant risk factor for COPD is Cigarette smoking. With the increase of cigarette smoking intensity there is an equivalent increase in the risk of COPD and the quantification of this risk is routinely done as pack-years. (One pack of cigarettes which is smoked per day for 1 year equals to 1 pack year). Male gender, cigarette smoking, low socioeconomic status, advanced age and occupational exposure are usually the independent risk factors contributing to COPD.

In about 10% of the general population it is found that the common sleep complaint is insomnia and it is chronically present. Insomnia is the term applied collectively to complaint involving the chronic inability to obtain adequate sleep. Three principal complaints commonly cited are: 1. Sleep onset insomnia (difficulty in falling asleep), 2. Frequent nocturnal awakening (interrupted sleep characterized by frequent awakenings) and 3. Early morning awakening (here the patient wakes up early in the morning and is not able to fall back asleep). The insomnia symptoms prevalence was high in subjects who had COPD, this was reported by Klink and Quan. There are many additional evidences furnished by recent study for association between COPD and insomnia. There is decreased productivity and worsening of health related Quality of Life (QOL) due to Primary insomnia which is itself a major and crucial public health problem. Similarly, reduced QOL is an established consequence of insomnia. QOL is reduced in COPD patients.

In one small cross-sectional study, the prevalence of smoking was 35% (apnea–hypopnea index AHI>10) in OSA patients and on comparison in an unmatched group of patients (AHI <5) it was only 18% which was provided by the investigators. Smoking has an effect on insomnia which leads to disrupted sleep architecture including sleep deprivation characterized by sleep insufficiency and sleep fragmentation characterized by repetitive short interruptions of sleep.

The term “overlap syndrome” is used to describe patients with concomitant OSA and COPD.

Patients with overlap syndrome have an. There is an increased rate of hospitalization and mortality in patients who have overlap syndrome which is characterized by patient having both COPD and OSA as compared with COPD alone hence, the current study will be performed to estimate proportion of insomnia in chronic obstructive pulmonary diseases and to study the association of insomnia with severity of chronic obstructive pulmonary diseases among study participants.

2. Materials and Methods

This prospective observational study was conducted in Department of Respiratory Medicine of Dr. Vasantrao Pawar Medical College, Hospital and Research Centre, Nashik, Maharashtra, India. Written informed consent was taken from all the study participants and those who give consent were enrolled in the present study. Total 159 COPD patients were included in the study after satisfying the eligibility criteria. The COPD Patients which were enrolled after satisfying the eligibility criteria given GSAQ Questionnaire to find the presence of insomnia, PSQI for sleep quality and then SF-36 score questionnaire to assess Quality of Life. Study was conducted for a duration of 2 years (August 2018 to December 2020).

2.1 Study Setting

Study will be conducted in OPD and IPD of Department of Respiratory Medicine at a tertiary health care institute.

2.2 Duration of Study

August 2018 to December 2020.
- Study Participants
- Sample Size – 159

2.3 Formula for Sample Size Calculation

Sample size for one proportion = \( \frac{Z^2(P \times Q)}{L^2} \)

Where, \( Z = \) critical value = 1.96
\( P = \) proportion of patients = 12%
\( Q = (1-P) \)
\( L = \) Allowable error = 0.05
2.4 Eligibility Criteria

2.4.1 Inclusion Criteria

- Age group $\geq 40$ years irrespective of gender with diagnosed COPD cases.
- Patients giving informed consent.
- Patients with insomnia with (1) sleep onset insomnia (difficulty in falling asleep),
- Frequent nocturnal awakening (interrupted sleep characterized by frequent awakenings).
- Early morning awakening (here the patient wakes up early in the morning and is not able to fall back asleep).

2.4.2 Exclusion Criteria

- Patients having past history of any other pulmonary diseases.
- Patients having medical ailments that could result in disturbed sleep such as OSA, symptomatic heart failure, significant chronic pain, nocturia (where in average is $>4$ times/night) restrictive lung disease, shift work, anyone with a history which is consistent with a sleep disorder other than insomnia and history of depression;
- If there is inability to obtain informed consent from patients.
- If patients has mental retardation.

2.4.3 Clinical Criteria

The diagnosis of COPD was considered in patient based on Global Initiative for Chronic Obstructive Pulmonary Disease (GOLD) guidelines (2018). The Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria was used to categorize severity\(^{13}\). Dyspnea severity was assessed using the Medical Research Council dyspnea scale\(^{14}\).

3. Observations and Results

Table 1. Age group distribution

<table>
<thead>
<tr>
<th>Age group</th>
<th>Frequency</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>40 to 50 years</td>
<td>46</td>
<td>29</td>
</tr>
<tr>
<td>51 to 60 years</td>
<td>67</td>
<td>42</td>
</tr>
<tr>
<td>more than 60 years</td>
<td>46</td>
<td>29</td>
</tr>
<tr>
<td>Total</td>
<td>159</td>
<td>100</td>
</tr>
</tbody>
</table>

As seen in the above table, the most common age group amongst study population was 51 to 60 years (42%) followed by 40 to 50 years (29%) and more than 60 years (29%).

Table 2. Gender distribution

<table>
<thead>
<tr>
<th>Gender</th>
<th>Frequency</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>72</td>
<td>45.5</td>
</tr>
<tr>
<td>Male</td>
<td>87</td>
<td>54.5</td>
</tr>
<tr>
<td>Total</td>
<td>159</td>
<td>100</td>
</tr>
</tbody>
</table>

As seen in the above table, there was male predominance (54.5%) in the study population as compared to females (45.5%).

Table 3. Occupation

<table>
<thead>
<tr>
<th>Occupation</th>
<th>Frequency</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Housewife</td>
<td>17</td>
<td>11</td>
</tr>
<tr>
<td>Business</td>
<td>19</td>
<td>12</td>
</tr>
<tr>
<td>Shopkeeper</td>
<td>37</td>
<td>23</td>
</tr>
<tr>
<td>Driver</td>
<td>30</td>
<td>19</td>
</tr>
<tr>
<td>Construction</td>
<td>11</td>
<td>7</td>
</tr>
<tr>
<td>Farmer</td>
<td>45</td>
<td>28</td>
</tr>
<tr>
<td>Total</td>
<td>159</td>
<td>100</td>
</tr>
</tbody>
</table>
As seen in the above table, the most common occupation amongst study population was farmer (28%) followed by Shopkeeper (23%) and Driver (19%).

**Table 4. Body Mass Index**

<table>
<thead>
<tr>
<th>BMI</th>
<th>Frequency</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underweight</td>
<td>10</td>
<td>6.1</td>
</tr>
<tr>
<td>Normal</td>
<td>46</td>
<td>28.8</td>
</tr>
<tr>
<td>Obese</td>
<td>104</td>
<td>65.2</td>
</tr>
<tr>
<td>Total</td>
<td>159</td>
<td>100</td>
</tr>
</tbody>
</table>

As seen in the above table, most of the study population were obese (65.2%) followed by normal BMI (28.8%) and underweight (6.1%).

**Table 5. Grade of MMRC dyspnea**

<table>
<thead>
<tr>
<th>MMRC Grade</th>
<th>Frequency</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>22</td>
<td>14</td>
</tr>
<tr>
<td>Grade 2</td>
<td>57</td>
<td>36</td>
</tr>
<tr>
<td>Grade 3</td>
<td>54</td>
<td>34</td>
</tr>
<tr>
<td>Grade 4</td>
<td>25</td>
<td>16</td>
</tr>
<tr>
<td>Total</td>
<td>159</td>
<td>100</td>
</tr>
</tbody>
</table>

As seen in the above table, most of the study population were grade 2 dyspnea (36%) followed by Grade 3 (34%) and Grade 4 (16%).

**Table 6. Severity of COPD according to GOLD criteria**

<table>
<thead>
<tr>
<th>GOLD FEV1</th>
<th>Frequency</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>10</td>
<td>6.1</td>
</tr>
<tr>
<td>Moderate</td>
<td>72</td>
<td>45.5</td>
</tr>
<tr>
<td>Severe</td>
<td>43</td>
<td>27.3</td>
</tr>
<tr>
<td>Very severe</td>
<td>34</td>
<td>21.2</td>
</tr>
<tr>
<td>Total</td>
<td>159</td>
<td>100</td>
</tr>
</tbody>
</table>

As seen in the above table, most of the study population were Moderate COPD (45.5%) followed by severe COPD (27.3%) and Very severe (21.2%).

**Table 7. Comorbidity**

<table>
<thead>
<tr>
<th>Comorbidities</th>
<th>Frequency</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>17</td>
<td>11</td>
</tr>
<tr>
<td>Hypertension</td>
<td>45</td>
<td>28</td>
</tr>
</tbody>
</table>

As seen in the above table, Comorbidities like Diabetes and Hypertension was observed in 11% and 28% of study population respectively.

**Table 8. Ex smoker**

<table>
<thead>
<tr>
<th>Ex smoker</th>
<th>Frequency</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>113</td>
<td>71</td>
</tr>
<tr>
<td>Yes</td>
<td>46</td>
<td>29</td>
</tr>
<tr>
<td>Total</td>
<td>159</td>
<td>100</td>
</tr>
</tbody>
</table>

As seen in the above table, 29% of study population was ex smokers.

**Table 9. Pack years**

<table>
<thead>
<tr>
<th>Pack years</th>
<th>Frequency</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 20</td>
<td>14</td>
<td>30.43</td>
</tr>
<tr>
<td>More than 20</td>
<td>32</td>
<td>69.57</td>
</tr>
<tr>
<td>Total</td>
<td>46</td>
<td>100.00</td>
</tr>
</tbody>
</table>

As seen in the above table, 69.57% of ex smokers had more than 20 pack years while 30.43% had less than 20 pack years.
Table 10. Prevalence of insomnia

<table>
<thead>
<tr>
<th>Prevalence of insomnia</th>
<th>Frequency</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>68</td>
<td>43</td>
</tr>
<tr>
<td>No</td>
<td>91</td>
<td>57</td>
</tr>
<tr>
<td>Total</td>
<td>159</td>
<td>100</td>
</tr>
</tbody>
</table>

As seen in the above table, the prevalence of insomnia in our study population was 43%.

Table 11. Prevalence of insomnia vs. severity of COPD

<table>
<thead>
<tr>
<th>Severity of COPD</th>
<th>Insomnia</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Mild</td>
<td>4 (6%)</td>
<td>6 (7%)</td>
</tr>
<tr>
<td>Moderate</td>
<td>13 (19%)</td>
<td>59 (65%)</td>
</tr>
<tr>
<td>Severe</td>
<td>27 (40%)</td>
<td>16 (18%)</td>
</tr>
<tr>
<td>Very severe</td>
<td>24 (35%)</td>
<td>10 (11%)</td>
</tr>
<tr>
<td>Total</td>
<td>68 (100%)</td>
<td>91 (100%)</td>
</tr>
</tbody>
</table>

As seen in the above table, the prevalence of insomnia was most commonly observed in severe COPD (40%) followed by Very severe COPD (35%), Moderate COPD (19%) and mild COPD (6%) and the difference was statistically significant.

Table 12. Prevalence of insomnia vs. Quality of Life

<table>
<thead>
<tr>
<th>SF 6</th>
<th>Insomnia</th>
<th>Yes</th>
<th>No</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical health score</td>
<td>32.54 ± 12.41</td>
<td>95.9 ± 33.49</td>
<td>0.0010</td>
<td></td>
</tr>
<tr>
<td>Mental health score</td>
<td>54.89 ± 14.56</td>
<td>86.56 ± 29.35</td>
<td>0.0010</td>
<td></td>
</tr>
</tbody>
</table>

As seen in the above table, mean Physical health score and mental health score was significantly lower in insomnia patients as compared to non insomnia patients.

Table 13. Prevalence of insomnia vs. PSQI

<table>
<thead>
<tr>
<th>PSQI</th>
<th>Insomnia</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSQI 8.0 ± 2.7</td>
<td>3.2 ± 2.1</td>
<td></td>
<td>0.0010</td>
</tr>
</tbody>
</table>

As seen in the above table, mean PSQI was significantly higher in insomniac patients as compared to non insomniac patients.

4. Discussion

Chronic Obstructive Pulmonary Disease (COPD) is a disease which is chronic and progressive which is characterized by a decline in respiratory function, exercise capacity and health status which is inevitable. The prevalence of COPD is increasing worldwide as is tobacco usage.

In about 10% of the general population it is found that the common sleep complaint is insomnia and it is chronically present. There is decreased productivity and worsening of health related Quality of Life (QOL) due to Primary insomnia which is itself a major and crucial
public health problem. However, nearly little attention and importance has been given to insomnia in medical disorders which includes Chronic Obstructive Pulmonary Disease (COPD).

4.1 Age group
In the present study, the most common age group amongst study population was 51 to 60 years (42%) followed by 40 to 50 years (29%) and more than 60 years (29%). Similarly in the study conducted by the Asif Hasan et al., maximum number of patients of COPD had their onset of disease in between 41-50 years. Guleria et al., have reported similar findings in their study where the maximum number of patients had age of onset between 40-70 years. This findings is in agreement with the study by Narayana Gowda et al., in which out of one hundred and seven (107) patients, the most common age group was 55 to 65 years (40.19%). The next common age group was 65 to 75 years (32.71%). This is because it was more commonly seen in patients who had lung disease which was advanced. This expresses and shows at the bronchial mucosal level that there is marked deterioration in host defenses.

4.2 Gender
In the present study, there was male predominance (54.5%) in the study population as compared to females (45.5%). COPD is a male dominant disease, due to higher prevalence of smoking in male gender and also males are more susceptible to smoking than females. Hence there is high prevalence of COPD in males. This findings correlate well with the study conducted by Niranjan Mambally Rachiah et al., in which males accounted for 88%, with a male-female ratio of 6.33:1. In the present study all males were smokers, 6 female patients were non-smokers but all of them were exposed to smoke of burnt fuels which is very common in rural Indian population. In this part of the country which is rural India, cooking is mainly done by using wood and cow dung. This is possibly a strong risk factor for development of COPD among female patients. This findings is in agreement with the study by Narayana Gowda et al., in which out of 107 patients, 72 were male patients.

4.3 Occupation
In the present study, the most common occupation amongst study population was Farmer (28%) followed by Shopkeeper (23%) and Driver (19%).

4.4 BMI
In the present study, most of the study population were obese (65.2%) followed by normal BMI (28.8%) and underweight (6.1%).

4.5 Dyspnea
In the present study, most of the study population were grade 2 dyspnea (36%) followed by Grade 3 (34%) and Grade 4 (16%). Similarly in the study conducted by Sunil Babu M et al., 100% of the patients presented with breathlessness and cough. Many had peripheral edema and distension of the abdomen. Padmavathi et al., reported dyspnea in 100%, pedal edema in 90.4% and cyanosis in 83.2% of group.

4.6 Severity of COPD
In the present study, most of the study population were Moderate COPD (45.5%) followed by severe COPD (27.3%) and Very severe (21.2%). This findings is in agreement with the study conducted by Ladeira et al., in which GOLD stage B (50%) followed by GOLD stage C (28%).

4.7 Comorbidities
In the present study, comorbidities like Diabetes and Hypertension was observed in 11% and 28% of study population respectively. This findings is in agreement with the study by Abraham M Ittyachen et al., in which 9 (27.1%) had diabetes mellitus, 20 patients (28.6%) had hypertension.

4.8 Smoking
In the present study, 29% of study population were Ex-smokers in which 69.57% of ex-smokers had more than 20 pack years while 30.43% had less than 20 pack years. Similarly the study by Narayana Gowda et al., in which out of seventy two (72) 45 (62.5%) were smokers and twenty seven (27) (37.5%) were non-smokers.
4.9 Prevalence of Insomnia

In the present study, the prevalence of insomnia in our study population was 43%. The prevalence of insomnia was most commonly observed in severe COPD (40%) followed by Very severe COPD (35%), Moderate COPD (19%) and mild COPD (6%) and the difference was statistically significant. Similarly in the study conducted by Rohit Budhiraja et al. there was no difference in FEV1 value among participants with insomnia (48.9% predicted) or those without insomnia (44.7% predicted, P = 0.17). In different GOLD stages of COPD the prevalence of insomnia was not significantly different. In various studies it was found out that about 34%–78% is the estimated prevalence of disturbed sleep in COPD patients. Study by Sameer Vaidya et al. found that the prevalence of sleep disorders in COPD was 66 out of which 31% had an overlap of two or more disorders. The prevalence in COPD patients was significantly higher than the healthy adults (P < 0.001). In COPD the most common sleep disorder was found to be insomnia, whereas it was shown that a healthy population may have disturbed sleep by GSAS and this disturbed sleep was commonly due to anxiety/depression. The prevalence of disturbed sleep varied between 20.0% and 34.2% in a study on a healthy population from South India and in our study, it was 16%34. Sameer Vaidya et al. also reported that patients have a higher propensity of developing sleep disorder those who have a lower FEV1. Some previous studies have also found that patients having more severe COPD also have worse sleep have been found in some previous studies.

4.10 Quality of Life vs. Insomnia

In the present study, mean Physical health score and Mental health score was significantly lower in insomnia patients as compared to non-insomnia patients. The QoL of patients with COPD may therefore be influenced by the quality of sleep, as observed by a previous study conducted on a small sample. A consecutive survey concluded that the predictor of poor QoL in patients with COPD is poor sleep quality as measured with both specific and generic tools. QoL decreases when sleep disorders increase this was found and confirmed by Akinci and Yildirim (2013). In the present study, mean PSQI was significantly higher in insomniac patients as compared to non-insomnia patients. This findings was comparable with the study conducted by Lucia Dignani et al. Sleep was altered (PSQI > 5) in 83.3% of subjects with COPD. This percentage is greater than the percentages of other studies which ranged between 75% and 78%.

5. Conclusion

40% of our patients with COPD experienced poor sleep quality. Presence of insomnia in patients with COPD is also associated with increased daytime sleepiness and worse QOL. Considering the disease burden of COPD and insomnia, these results have important clinical and public health implications. In order to ascertain the causality of factors associated with insomnia in patients with COPD prospective studies need to be designed.

6. References


**Abbreviations**

AVAPS - Average Volume Assured Pressure Support
Auto-PEEP – Auto Positive End Expiratory Pressure
Ahi – Apnea Hypopnea Index
Bilevel PAP - Bilevel Positive Airway Pressure
BMI – Body Mass Index
CAT – COPD Assessment Test
CBT I – Cognitive Behavioural Therapy for Insomnia
CDRQ - Chronic Respiratory Disease Questionnaire
COPD – Chronic Obstructive Pulmonary Disease
CRP - C Reactive Protein
CPAP - Continuous Positive Airway Pressure
DSM 4 – Diagnostic and Statistical Manual of Mental Disorders - 4
E-selectin –CD62 Antigen like Family Member E
EPESE questionnaire– Established Populations for Epidemiologic Studies of the Elderly
FEV 1 – Forced Expiratory Volume During First Second
FVC – Forced Vital Capacity
FRC - Functional Residual Capacity
GSQ – Global Sleep Assessment Questionnaire
GOLD – Global Initiative for Chronic Obstructive Lung Disease
GERD – Gastroesophageal Reflux Disease
HIF-1 - Hypoxia Inducible Factor-1 Pathway
IRLSSG - International Restless Legs Syndrome Study Group
iVAPS - Intelligent Volume Assured Pressure Support
IL-6 - Interleukin 6
ICAM-1 - Intracellular Adhesion Molecule-1
INS group – Individuals with Insomnia
IL-8 – Interleukin 8
LLN – Lower Limits of Normal
MT receptor - Melatonin Receptor
Mmrc dyspnea scale – Modified Medical Research Council Dyspnea Scale
NIPPPV - Nocturnal Intermittent Positive Pressure Ventilation
Or - Odds Ratio
OSA – Obstructive Sleep Apnea
PSG- Polysomnography
PSQI – Pittsburgh Sleep Quality Index
PETCO2 - End Tidal Carbon Dioxide
Pcrit - Passive Critical Closing Pressure
Qol – Quality of Life
REM – Rapid Eye Movement
RLS - Restless Leg Syndrome
SaO2 – Oxygen Saturation
Sdv - Sleep Disordered Breathing
SSRI – Selective Serotonin Reuptake Inhibitors
SF-36 Questionnaire – Short form 36 Health Survey Questionnaire
Sgrq- St. George’s Respiratory Questionnaire
tcPCO2 - Transcutaneous PCO2
TNF-α - Tumor Necrosis Factor alpha
VEGF - Vascular Endothelial Growth Factor
VCAM-1 – Vascular Cell Adhesion Molecule-1

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