Prevalence, risk factors and effects of restless legs syndrome in COPD patients

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Abstract

Restless legs syndrome (RLS), a sensory motor disorder, is commonly seen amongst chronic obstructive pulmonary disease (COPD) patients. We conducted a study to know its prevalence in COPD and analyse the possible cause and effect of RLS. It is an analytical cross-sectional study conducted between July 2016-December 2020.The prevalence of RLS was evaluated in patients of COPD using RLS diagnostic criteria. Spirometry, iron profile and arterial blood gas analysis was performed in all the patients to evaluate the cause of RLS. The effect was evaluated with diagnostic criteria for insomnia and patient health questionnaire (PHQ2) for depression. There were 205 participants with a mean age of 59±8 years, 182 (88.7%) men and 23 (11.2%) women. The mean body mass index (BMI) was 29±3.9 kg/m^2. The prevalence of RLS was 31.2%. RLS was more common amongst women compared to men (60.8% *vs* 27.4%). RLS was more prevalent among hypoxemic (PaO_2<60 mm Hg) and hypercapnic ($PaCO_2$>45 mm Hg) patients (p<0.016; p<0.017). The ROC curve plotted between PaO_2 and RLS occurrence showed that the patients having PaO_2 less than 76 mm of Hg were more prone to develop RLS. RLS patients had a higher incidence of insomnia as compared to those without RLS (68.8% *vs* 36.8%, p<0.001). COPD with RLS patients had more depressive symptoms with a higher patient health questionnaire 2 (PHQ2) score (35.9% *vs* 14.2%, p<0.001) compared to non RLS COPD patients. The multiple regression analysis also confirmed that RLS led to insomnia and depressive symptoms in COPD patients. To conclude, RLS is common in COPD patients. RLS leads to insom-nia and depression, thus should be identified and treated.

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Introduction

In 1945, the Swedish neurologist Ekbom described a condition that he named restless legs syndrome (RLS) [1]. Population-based studies using the full standard diagnostic criteria for RLS report a prevalence of 5% to 10% from both India and abroad [2-4]. The cause of RLS is unknown, it may be idiopathic or secondary to other disorders. Idiopathic RLS appears to run in families, suggesting a genetic basis. Secondary RLS may be associated with various diseases. RLS is known to be more prevalent in chronic obstructive pulmonary disease (COPD). The prevalence of RLS is shown to be higher in comparative studies between those with COPD than those without COPD [5-7]. There are no Indian studies evaluating RLS in Indian COPD patients [8].

The diagnosis of RLS is clinical, based on URGE criteria (U = Urge to move the legs, usually associated with unpleasant legs sensations; R = Rest induces symptoms; G = Gets better with activity (any movement e.g. walking, stretching); E = Evening and night accentuation) [8]. Though the exact pathogenesis of RLS is not known, clinical observations suggest the role of dopaminergic pathway as dopaminergic drugs alleviate the symptoms and dopamine antagonists trigger or exacerbate them [9]. The impairment in dopaminergic system is thought to be functional and metabolic rather than anatomical. The functional abnormality is thought to be hypoxia through the hypoxia inducible factor-1 pathway [10]. But its association with various clinical and laboratory findings of COPD are not very clear. To the best of our knowledge, no study has thoroughly evaluated the cause and the effect of RLS in COPD patients.

The aims of the study were: i) To find the prevalence of RLS in COPD patients. ii) To find out if RLS in COPD patients correlate with forced expiratory volume in one second (FEV_1), serum ferritin level, daytime partial pressure of oxygen (PaO_2) and daytime partial pressure of carbon dioxide ($PaCO_2$). iii) To evaluate the presence or absence of insomnia and depression in COPD patients with and without RLS.

Materials and Methods

This is a descriptive analytical cross-sectional study, conducted between July 2016 to December 2020 after taking an institutional ethical committee approval. Stable COPD patients with a written and informed consent were enrolled in the study. The study was conducted in a tertiary care institute in Delhi on patients following up in an outpatient department of Pulmonary, Sleep and Critical Care Medicine. The sample size was calculated using the formula: $n = (Z^2 \times P \times (1 - P))/e^2$; where Z = value from standard normal distribution corresponding to desired confidence level (Z=1.96 for 95% CI), where P is expected true proportion and e is desired precision. Considering the prevalence of RLS in COPD patients as 30% (prior literature shows prevalence of RLS in COPD patients varies from 29.1% to 36.8%), precision of 5%, a minimum sample size was calculated to be 189 [5,6]. Considering some attrition of 8% a sample size of 204 was required.

The patients were diagnosed with COPD on the basis of history, clinical features, imaging and pulmonary function test, according to the Global initiatives for Chronic Obstructive Lung Disease (GOLD) guideline criteria [11]. RLS was diagnosed on the basis of history of "URGE" (described earlier) [12]. Other causes like myalgia, legs cramps, arthritis, etc were ruled out. The diagnosis was made by a pulmonologist with a sleep expertise. It was confirmed by a neurologist in case of doubt.

The patients were evaluated in detail with history, clinical examination and routine biochemical test. The exclusion criteria were hospitalised patients, those having exacerbation, secondary RLS due to comorbid disorder (uncontrolled diabetes, uraemia due to chronic kidney disease, rheumatoid arthritis, neurological disorder), recent hospitalization, medication that increases RLS and pregnancy. The details of illness, comorbidities i.e. type 2 diabetes mellitus, hypertension, ischemic heart disease and hypothyroidism were recorded. The routine investigations, chest radiograph findings were entered in a proforma. None of the patients were on long term oxygen therapy.

A spirometry, iron profile, oxygen saturation and blood gas analysis were performed in all the patients after inclusion. Spirometry was performed using computer based Medisoft/Morgan Scientific Spiro Airin®machine, as per American Thoracic Society (ATS) guidelines [13] .The best of three consecutive tests was used in analysis. Forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), and their percentage ratio FEV_1/FVC were measured. Blood oxygen saturation was recorded using finger pulse-oximetry. The partial pressure of arterial oxygen (PaO_2), partial pressure of arterial carbon dioxide ($PaCO_2$) and pH were analysed in the blood sample drawn from the radial artery. The body mass index (BMI) assessment was done using the Asian criteria [14]. The patients were additionally evaluated for insomnia. Insomnia was diagnosed as per the Diagnostic and Statistical Manual of Mental Disorders (V) [15]. It was defined by difficulty falling asleep, staying asleep, waking up too early, or having non-refreshing sleep despite adequate opportunity and circumstances to sleep and it results in some form of daytime impairment [15-17]. The patients were screened for depression too with the help of patient health questionnaire -2 (PHQ2) [18].

Statistical analysis

The prevalence of RLS among COPD population was calculated. The data were entered in the MS EXCEL spreadsheet, coded appropriately. Analysis was carried out using SPSS (Statistical Package for Social Sciences) v23.0. Categorical data were presented as percentage (%). Chi square test was used to evaluate differences between groups for categorized variables. All tests were performed at 5% level of significance. A p-value <0.05 was considered significant.

The correlation between PaO_2 and presence of RLS was calculated using Spearman Rank method. A receiver operating characteristic (ROC) curve was plotted between PaO_2 and occurrence of RLS. Multivariate logistic regression was applied to know the predictors / risk factors of insomnia and depressive symptoms in our study group.

Results

A total of 205 individuals participated in the study; 182 (88.7%) were men and 23 (11.2%) women. The age of the study participants varied from 38 years to 77 years, the mean age being 59±8 years. The mean height of the study participants was 161±7.8 cm. The mean weight was 56.6 kg±13.9. The mean BMI was 21.6 kg/m^2. The mean haemoglobin was 13.2±1.76 gm/dl. Table 1 describes the demographics of the study population between the two groups of RLS and non RLS COPD patients. COPD disease severity was similar in both the

Table 1. Demographic parameters of the study subjects.

Parameters	Number of subgroup population (N)	RLS absent (n=141), n (%)	RLS present (n=64), n (%)	p-value
Gender				
Male	182	132 (93.6%)	50 (78.1%)	<0.001
Female	23	09 (6.38%)	14 (21.8%)	
Age Group (years)				
<50	28	15 (10.6%)	13 (20.13%)	<0.290
51-60	85	60 (42.6%)	25 (39.1%)	
61-70	77	56 (39.7%)	21 (32.8%)	
71-80	15	10 (7.09%)	05 (7.81%)	
BMI				
Underweight (<18.5 kg/m^2)	52	43 (30.5%)	09 (14.1%)	<0.040
Normal (18.5-23.0 kg/m^2)	94	60 (42.6%)	34 (53.1%)	
Overweight and obese (>23 kg/m^2)	59	38 (26.9%)	21 (32.8%)	

RLS, restless legs syndrome; BMI, body mass index.

groups. FEV_1 was 47.03±16.28% *vs* 46.9±16.53% (p<0.484) in COPD patients with RLS and without RLS, respectively.

Out of the 205 participants, 64 participants were found to have RLS. Thus, the prevalence of RLS in COPD was found to be 31.2%. The prevalence of RLS in different subgroup study subjects is shown in Table 2. The gender wise distribution of RLS among COPD patients was found to be statistically significant (p < 0.001) with males having lower prevalence of RLS (27.4%) compared to females (60.8%). The study participants were grouped into two age categories. The prevalence of RLS among patients ≤ 60 years was 33.6% and those above 60 years had a prevalence of 28.3%. The prevalence of RLS among hypoxic COPD patients was 38.5% and among hypercapnic subjects was 47.4%. The patients who had both hypoxia and hypercapnia had a prevalence of RLS 56.2%. Underweight participants had a RLS prevalence of 17.3% while those with high BMI had a prevalence of 35.6% (Table 2). Twenty nine i.e. 14.1% COPD patients had excessive daytime sleepiness (EDS); 12.5% (8/64) of RLS patients and 14.9% (21/141) non RLS patients had EDS (p<0.649). Table 3 shows the difference in various parameters (quantitative and qualitative) in patients who had RLS compared to those without. There was no significant difference between the two groups in terms of serum ferritin, serum iron, FEV_1 and presence of any comorbidity (p=0.330; p<0.079; p<0.900; p<0.828 respectively) (Table 3). When the arterial blood gas analysis values were compared, the mean PaO_2 was significantly lower in RLS patients compared to non RLS patients (71.2 *vs* 74.7 mmHg, p value 0.034). Hypoxia (PaO_2<60) was more prevalent among RLS patients than non RLS patients (65.6 vs 47.5%; p<0.016). Similarly, the mean $PaCO_2$ was significantly higher in RLS patients compared to non RLS patients (40.3 *vs* 37.4 mmHg, p<0.012). Hypercapnia (PaCO2>45) was twice more common among RLS patients (28.1 *vs* 14.2%; p<0.017) (Table 3). RLS was more prevalent among patients who were both hypoxic and hypercapnic compared to those who were only hypoxic or hypercapnic (56.2 *vs* 38.5 *vs* 47.4%, respec-

Table 2. Prevalence of restless legs syndrome among different subtype population in the study.

Subgroup population	Number of subjects having RLS in subgroups (n/N)	Prevalence of RLS
Males	50/182	27.4%
Females	14/23	60.8%
Age ≤60 years	38/113	33.6%
Age >60 years	26/92	28.3%
BMI <18.5	9/52	17.3%
BMI >18.5 <23	34/94	36.2%
BMI >23	21/59	35.6%
Hypoxic subjects (PaO_2 <60)	42/109	38.5%
Hypercapnic Subjects ($PaCO_2$ >45)	18/38	47.4%
Hypoxic and hypercapnic subjects (PaO_2 <60; $PaCO_2$ >45)	9/16	56.2%

RLS, restless legs syndrome; BMI, body mass index; PaO_2, partial pressure of oxygen; $PaCO_2$, partial pressure of carbon dioxide; n, number of subjects in subgroup population having RLS; N, total number subjects in subgroup population.

Table 3. Quantitative variables ($PaCO_2$, PaO_2, serum ferritin, serum iron, FEV_1) and qualitative variables (hypoxia, hypercapnia, low FEV_1, insomnia, PHQ2 score and presence of comorbidity) among RLS and non RLS patients.

Parameters	RLS absent (n= 141) n (%)	RLS present (n=64) n (%)	p-value
$PaCO_2$ (mean±SD)	37.4±7.54	40.3±8.97	0.012
PaO_2 (mean±SD)	74.7±11.51	71.2±11.67	0.035
Serum ferritin (mean±SD)	44.38±16.5	51.8±43.6	0.333
Serum iron (mean± SD)	142.12±189.3	75.26± 46.2	0.079
FEV_1 (mean±SD)	47.4±16.9	47.7±16.4	0.450
FEV_1 ≥50% predicted (stage I and II) FEV_1<50% predicted (stage III and IV)	78 (55.3%) 63 (44.7%)	36 (56.2%) 28 (43.8%)	p=0.900
PaO_2 <60 (hypoxia) PaO_2 ≥60 (non-hypoxia)	67 (47.5%) 74 (52.5%)	42(65.6%) 22(34.4%)	p<0.016
$PaCO_2$ <45 (no hypercapnia) $PaCO_2$ >45 (hypercapnia)	121 (85.8%) 20 (14.2%)	46 (71.9%) 18 (28.1%)	p<0.017
Insomnia present Insomnia absent	52 (36.8%) 89 (63.1%)	44 (68.8%) 20 (31.25%)	p<0.001
PHQ_2 (≥3) PHQ_2 (<3)	20 (14.2%) 121 (85.8%)	23 (35.9%) 41 (64.1%)	p<0.001
Comorbidity present Comorbidity absent	66 (46.8%) 75 (53.2%)	31(48.4%) 33 (51.6%)	p=0.828

RLS, restless legs syndrome; FEV_1, forced expiratory volume in 1 second; COPD, chronic obstructive lung disease; PaO_2, partial pressure of oxygen; $PaCO_2$, partial pressure of carbon dioxide; PHQ_2, patient health questionnaire-2; SD, standard deviation.

tively). The presence of any comorbidity was evaluated for the occurrence of RLS, but no significant difference was found (Table 3). We also plotted the ROC curve (Figure 1) between PaO_2 and RLS occurrence. There was a statistically significant negative correlation between PaO_2 and presence of RLS by Spearman Rank method (r= -0.171; p=0.014). Through the ROC curve a cut off value of PaO_2 was determined which was 76 mm of Hg for the presence of RLS. The patients having PaO_2 less than 76 mm of Hg were prone to have RLS. We also found that 68.8% (44/64) of the RLS patients had insomnia whereas only 36.8% of non RLS patients had insomnia, the difference was found to be statistically significant (p<0.001) (Table 3). Presence and absence of hypoxia and hypercapnia and RLS was evaluated for the occurrence of insomnia via univariate analysis. The presence of RLS was statistically significant for the occurrence of insomnia (Table 4). When various parameters (age, gender, PaO_2, $PaCO_2$, RLS and depression) were subjected to multiple logistic regression, with an attempt to find out the predictor of insomnia, presence of RLS and depression was found to be significant risk factor of insomnia (p<0.003, p<0.001, respectively) (Table 5). The occurrence of RLS did affect the mood. Patients with RLS had a higher PHQ2 score compared to non RLS COPD patients (p<0.001). PHQ2 score ≥3 was seen in 35.9% of RLS patients and in 14.2% of non RLS patients. In univariate analysis insomnia and presence of RLS were found to be statistically significant for occurrence of depression (Table 4). When multiple logistic regression model was applied for knowing the predictors or risk factors of

Table 4. Univariate analysis for predictors of insomnia and depression.

	Insomnia present (n=96)	Insomnia absent (n=109)	p-value
Pa O_2 <60	6 (6.25%)	15 (13.8%)	p=0.077
Pa O_2 ≥60	90 (93.8%)	94 (86.2%)	
Pa CO_2 ≤45	78 (81.3%)	86 (78.9%)	p=0.67
Pa CO_2 >45	18 (18.8%)	23 (21.1%)	
Depression present	35	8	p<0.001
Depression absent	61	101	
RLS present	44 (45.8%)	20 (18.3%)	p<0.001
RLS absent	52 (54.2%)	89 (81.7%)	
	Depression present (n=43)	**Depression absent (n=157)**	
Pa O_2 <60	2 (46.5%)	19 (12.1%)	p=0.157
Pa O_2 ≥60	41 (95.3%)	138 (87.9%)	
Pa CO_2 >45	37 (86.0%)	123 (78.3%)	p=0.263
Pa CO_2 >45	6 (13.9%)	34 (21.6%)	
RLS present	23 (53.5%)	37 (23.6%)	p<0.001
RLS absent	20 (46.5%)	120 (76.4%)	
Insomnia present	35 (81.4%)	59 (37.6%)	p<0.001
Insomnia absent	8 (18.6%)	98 (68.4%)	

RLS, restless legs syndrome; PaO_2, partial pressure of oxygen; $PaCO_2$, partial pressure of carbon dioxide.

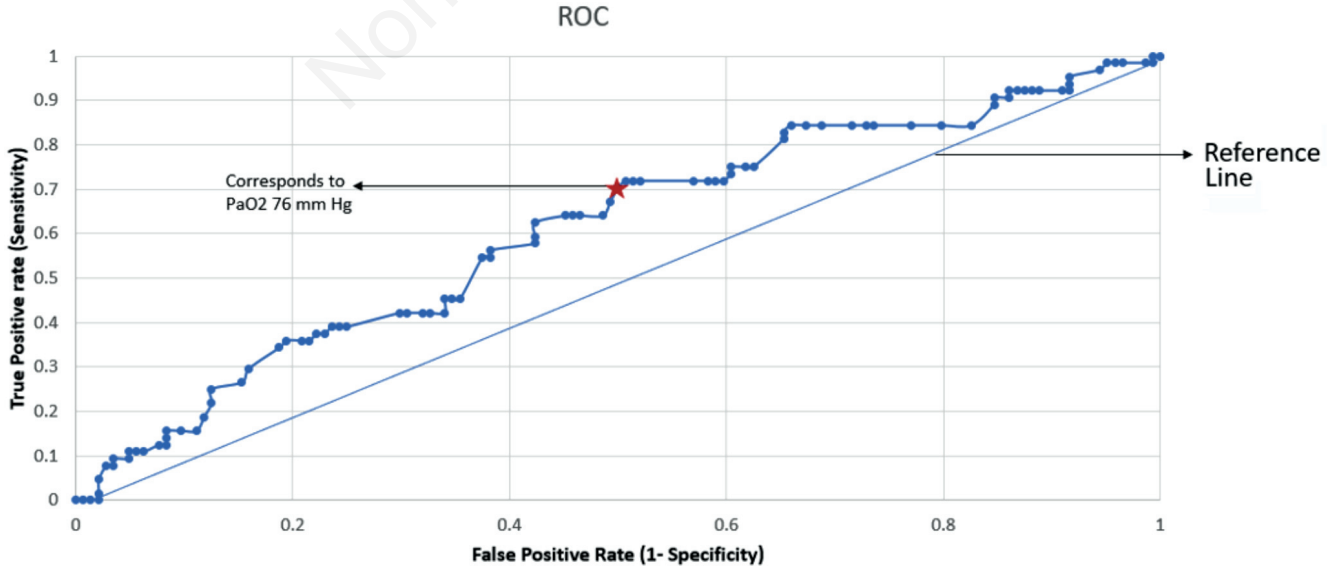

Figure 1. Receiver operative curve (ROC) between pO2 and presence of restless legs syndrome.

depression among COPD patients, presence of RLS and insomnia were found to be independent risk factors ($p<0.016$, $p<0.001$ respectively). Depression could be due to both RLS and COPD.

Discussion

To the best of our knowledge, this study is the first study from India on prevalence of RLS in COPD patients. Internationally also very few studies have evaluated the role of hypoxemia, hypercapnia and spirometry in COPD patients with RLS [5,6]. No study so far has evaluated the effect of RLS in COPD patients. We found that the prevalence of RLS was 31.2% in COPD patients based upon the diagnostic criteria. The epidemiological studies have suggested that RLS affects 2-10% of general population in western literature [19,20]. The prevalence in general population from India too is the similar [21]. The prevalence of COPD with RLS from western literature suggests that 29.1% to 36.8% of the COPD patients have RLS [5,6]. The prevalence of RLS has been shown to be higher even in comparative studies between those with COPD than those without COPD [5,6]. The importance of diagnosing RLS cannot be overemphasized, as RLS is associated with a poor quality of life [22]. COPD patients are known to have a poor quality of life and since RLS can make it worse, one needs to evaluate and treat it. Previous study by Ding *et al*. showed that chronic pulmonary disease (emphysema, chronic bronchitis and asthma) is an independent risk factor for RLS [23].

Previous studies have shown that there was no age difference between COPD with RLS and without RLS [5,6]. Similar to these studies, we found that there were no age differences between the two groups. Another finding was that RLS was evenly distributed in all age groups of COPD patients. RLS is known to occur in all age groups, hence we did not find any significant prevalence in any particular age group. Most studies have shown that RLS is more prevalent among women in the general population [3]. We observed that COPD with RLS was more common in women compared to men, though the number of women were low in our study. A study by Lo Coco *et al*. and Kaplan et al. have shown that the presence of RLS is independent of gender [5,6]. One more demographic finding of our study was that COPD with RLS was significantly more prevalent in overweight and normal weight patients compared to low BMI. In a population based study too it has been shown that RLS is commonly associated with obesity [24]. So age, gender and demography of RLS in COPD matches that of the general population. But in the study by Kaplan et. al showed no difference in BMI in COPD patients with RLS and without RLS [6].

The second major finding was that hypoxia and hypercapnia were more evident in COPD patients with RLS than without RLS. There was no correlation with lung function and RLS. Peripheral hypoxia has been shown to have a strong correlation with RLS even in non COPD subjects [25]. There is only one study to the best of our knowledge who have investigated the correlation of hypoxia and hypercapnia in COPD patients with RLS [6]. They also found that RLS is frequent in COPD, particularly in patients with severe hypoxemia/hypercapnia and in late stages of the disease. The exact mechanism of how hypoxia or hypercapnia can lead to RLS is not known. Kaycan *et al*. however have investigated neurophysiological changes in peripheral and central nervous system in COPD patient in moderate to severe hypoxemia and found that the airway obstruction may affect ponto medullary portion of brain [26]. Another possible mechanism is hypoxia, through the hypoxia inducible factor-1 (HIF-1) pathway, may lead to an increase in tyrosine hydroxylase and vascular endothelial growth factor (VEGF).Tyrosine hydroxy-

Table 5. Regression analysis for insomnia and depression.

Independent variables	Slope	Standard error	p-value	Lower 95% CI	Upper 95% CI
Multiple regression for insomnia					
Age	-0.0069	0.020	<0.731	0.954	1.033
Sex	-0.4551	0.562	<0.418	0.210	1.909
pO_2	0.001	0.003	<0.747	-0.006	0.008
pCO_2	-0.003	0.004	<0.532	-0.011	0.006
PHQ_2 score	0.106	0.018	<0.001	0.069	0.143
Presence of RLS	0.070	0.070	<0.003	0.074	0.351
Intercept	0.87932				
R-sq	0.2336				
p-value	<0.005				
Multiple regression for depression					
Age	0.008	0.022	0.724	0.964	1.053
Sex	-0.580	0.549	0.291	0.191	1.643
pO_2	0.004	0.003	0.157	-0.0016	0.0097
pCO_2	-0.003	0.004	0.462	-0.0099	0.0045
Insomnia	0.251	0.0557	<0.001	0.141	0.361
Presence of RLS	0.1453	0.0598	0.016	0.027	0.263
Intercept	1.4782				
R-sq	0.177				
p-value	<0.05				

RLS, restless legs syndrome; PaO_2, partial pressure of oxygen; pCO_2, partial pressure of carbon dioxide.

lase is a rate limiting enzyme in dopamine synthesis [17]. So, hypoxia due to deficit in dopamine synthesis possibly leads to RLS. A higher prevalence of RLS has been reported in other pulmonary disorders, too [17]. Similarly people living at a high altitude are also known to have a fourfold higher prevalence of RLS [27]. The level of hypoxia at which RLS is likely to occur is 76 mm of Hg in COPD patients. Though ROC for PaO_2 (Figure 1) did not have a good area under curve (AUC), studies with a larger sample size are required to exactly confirm the level of hypoxemia.

We also found that the COPD patients who had RLS had insomnia and higher PHQ2 score. No other study has investigated the role of RLS into development of insomnia and depressive symptoms in patients with COPD directly. Though a population based study on quality of life and nocturnal symptoms in a community based COPD cohort has shown that RLS was an independent predictor of poor sleep quality [28]. Lo Coco *et al*. has described that COPD patients who had RLS had excessive daytime sleepiness and insomnia complaints when compared to non-COPD RLS patients. They concluded that RLS is a cause of sleep disturbance in COPD patients [5]. Insomnia and depression are commonly seen with COPD. Lee *et al*. found that 35% of stable COPD patients in Asian population have sleep disturbance [29]. In multiple regression analysis we found that RLS is the only risk factor leading to insomnia and depressive symptoms in COPD patients. Insomnia is likely to be the effect rather than the cause of RLS in COPD like non COPD patients [30]. So there exists an association between RLS and insomnia. Similarly insomnia leads to depression as links between sleep and depression are strong [31]. The presence of insomnia and depression due to RLS can lead to further worsening of quality of life of COPD patients. Since RLS is treatable, it is important to evaluate the patients of COPD from RLS point of view. Through our study we aim to improve the awareness of RLS among chest physicians so that easily diagnosable and treatable parts of irreversible disease can be addressed and quality of life of COPD patients can be improved.

RLS treatment is based on the severity of RLS and the degree of disability. In mild and intermittent symptoms, lifestyle improvement is recommended. Mild exercise, limited caffeine intake, legs massage, hot baths may be beneficial [32]. It has been observed that about 20% RLS patients require drugs [8]. Pharmacological treatment is required in patients with disability and consists of dopaminergic agents such asropinirole, pramipexole, and rotigotine; α2 calcium channel ligands such as gabapentin and pregabalin; opioid agonist such as tramadol and methadone; and benzodiazepines [33]. In our patients, we prescribed pramipexole to those who did not improve with lifestyle modification.

There are many strengths of this study. This is the first study from India about prevalence of RLS in COPD patients. It has also evaluated the linkage between insomnia, depression and RLS in COPD patients. There were a few limitations of the study, too. We did not assess the severity and frequency of RLS symptoms, hence could not classify them as intermittent or chronic persistent RLS. The sample size was small; also, the quality of life due to RLS was not assessed.

Conclusion

To conclude, restless legs syndrome is common in Indian COPD patients, similar to Western population. In our study we found that the prevalence of RLS in COPD patients is 31.2%. RLS is more prevalent among hypoxic and hypercapnic patients. RLS was also found to be a risk factor for insomnia and depression hence, with possible reflection on the quality of life of these patients.

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