

Sleep Disorders in Patients with Parkinson's Disease during COVID-19 Pandemic: A Case–Control Study

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Abstract

Objective: To assess the impact of coronavirus disease 2019 (COVID-19) pandemic on sleep disorders among Parkinson's disease (PD) patients using validated questionnaires. **Materials and Methods:** This prospective study involved 50 PD patients and 50 age, gender, and body mass index-matched controls. All participants underwent assessment of cognition using Montreal Cognitive Assessment scale, sleep quality using Parkinson's disease sleep scale-2 (PDSS-2; for PD patients) and Pittsburgh Sleep Quality Index (PSQI; for PD patients and healthy controls), excessive daytime sleepiness (EDS) using Epworth sleepiness scale (ESS), insomnia symptoms and severity using insomnia severity index (ISI), restless legs syndrome (RLS) using International RLS Study Group criteria, rapid eye movement sleep behavior disorder (RBD) using RBD Single-Question Screen (RBD1Q), and depression using Patient Health Questionnaire-9 scale. **Results:** Eighty-eight percent of PD patients reported one or more sleep disorders, compared to 28% controls. While 72% of PD patients reported poor sleep quality (PDSS-2 ≥ 15 , PSQI > 5), 60% had insomnia, 58% reported RBD, 50% had EDS, and 36% reported RLS. Depressive symptoms were reported by 70% patients. PD patients with and without poor sleep quality were comparable with regards to demographic and clinical variables, except for depressive symptoms ($P < 0.001$). Depressive symptoms showed a significant association with EDS ($P = 0.008$), RBD ($P < 0.001$), and insomnia ($P = 0.001$). **Conclusion:** Prevalence of sleep disorders increased in PD patients during the COVID-19 pandemic. Prevalence of EDS, RBD, and RLS in PD patients was higher compared to that reported in studies during the pre-COVID-19 times. Presence of depressive symptoms was a significant correlate of presence of sleep disorders in PD patients.

Keywords: Excessive Daytime Somnolence, Parkinson's disease, rapid eye movement sleep behavior disorder, restless legs syndrome, sleep quality

INTRODUCTION

During the past 2 years, world has witnessed repeated lockdowns to contain the spread of the coronavirus disease 2019 (COVID-19) pandemic. During these periods, majority of the population remained confined to their homes, with lack of physical interactions.^[1] In addition to the direct impact of COVID-19–related pulmonary and extrapulmonary disorders, the lack of social interactions, erratic sleep–wake schedules, and heightened stress affected physiological activities including sleep in the general population.^[2] Several studies have reported worsening of sleep parameters in the general population during the COVID-19 pandemic.^[2–4]

Parkinson's disease (PD), the second most common chronic neurodegenerative disease, affects 1%–2% of all individuals over the age of 65 years.^[5,6] Although it is classically diagnosed by the presence of classical motor symptoms including bradykinesia, rest tremor, rigidity, and postural instability, patients often experience a variety of non-motor symptoms (NMS), which may remain unrecognized.^[7,8] Disturbed sleep is one of the most common NMS with a prevalence of up to 90%.^[9] It significantly affects the functionality and quality of life of both PD patients as well as their caregivers.^[9] However, Western literature cannot be extrapolated to Indian population suffering from PD for a number of reasons that include difference in sleep–wake

pattern, prevalence of sleep disorders in the Indian population, and racial differences observed in the quality of care to the patients suffering from PD.^[10,11]

A few studies from India have reported sleep disorders among patients with PD during the non-pandemic period. For example, prevalence of poor subjective sleep quality was found to range between 29% and 87%^[12–14] and nearly three-fourths of the patients with PD were found to suffer from insomnia.^[12,15,16] Similarly, prevalence of excessive daytime somnolence (EDS) in PD has been reported to be between 10% and 30% across studies.^[13,14,17] Restless legs syndrome (RLS), one of the potential determinants of poor sleep quality, has been reported by 8%–15% of PD patients.^[15,18,19] Lastly, a couple

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of studies from a single center examined prevalence of rapid eye movement sleep behavior disorder (RBD) and found it to vary between 20% and 25%.^[15,20] However, prevalence of poor sleep quality and RLS varied across available studies.^[12-15,18,19,21] Diagnostic criteria for RLS have been updated in 2014 by the International RLS Study Group (IRLSSG), and this change has an important bearing on the diagnosis of RLS.^[22] Thus, literature regarding prevalence of RLS among patients having PD before the publication of these criteria needs to be updated. Lastly, only three studies included the control group,^[13,18,19] with none of them having body mass index (BMI)-matched controls. Inclusion of control group is important due to limited literature regarding prevalence of sleep disorders in the Indian population.

Furthermore, COVID-19 pandemic has been reported to worsen various motor and non-motor features of PD.^[23,24] An online questionnaire-based pan-India survey during the initial months of COVID-19 pandemic reported significant sleep disturbances in more than one-third of the PD patients, with new-onset/worsening of sleep disturbances in 24% of PD patients.^[25]

Despite several works highlighting the plight of PD patients during the COVID-19 pandemic,^[26] to the best of our knowledge, scientific data addressing the impact of pandemic on prevalence of sleep disorders among PD patients is nonexistent, especially the one using validated screening or diagnostic questionnaires to assess sleep disorders. We hypothesized that prevalence of poor sleep quality, insomnia, and RBD would be greater in PD patients compared to that in the pre-pandemic period. Similarly, we also hypothesized that prevalence of RLS would change considering the updated criteria of RLS. Thus, this study was planned to assess prevalence of poor sleep quality, insomnia, EDS, RBD, and RLS in PD patients and compare it with age, gender, and BMI-matched healthy controls.

MATERIALS AND METHODS

PD patients were recruited from the Movement Disorder Clinic at a university hospital between October 2020 and April 2021 after getting approval from the Institutional Ethics Review Board. Included participants were 50 consecutive PD patients and 50 age, gender, and BMI-matched healthy controls with no clinical signs or symptoms of COVID-19 for past 3 months before recruitment. PD was diagnosed using Movement Disorders Society-Parkinson's Disease criteria. Patients aged ≥ 18 years, on stable dopaminergic therapy for the past 4 weeks, and having a bed partner or caregiver available for answering sleep-related questions were recruited. Exclusion criteria for patients included pregnancy; patients with features suggestive of Parkinson-plus syndromes, including progressive supranuclear palsy, multiple system atrophy, corticobasal degeneration, and diffuse Lewy body disease, and secondary parkinsonism; those on medications influencing sleep or interacting with dopaminergic system, including antidepressants, sedatives, hypnotics, antipsychotics, cannabis, opioids, and opiates, within 3 months of recruitment;

and lastly, patients with cognitive decline (Montreal Cognitive Assessment [MoCA] score < 24).

Hospital staff, friends, and relatives of the patients (excluding caregivers) who did not have any neurological, psychiatric, or medical illness affecting sleep were recruited as healthy controls. In addition to matching of the geographic location and social and educational status with PD patients, healthy controls were also age, gender, and BMI matched. Exclusion criteria for healthy controls included pregnancy; participants on medications influencing sleep or interacting with dopaminergic system, including antidepressants, sedatives, hypnotics, antipsychotics, cannabis, opioids, and opiates, within 3 months of recruitment; and those with cognitive decline (MoCA score < 24). Written informed consent was obtained from all participants before including them in the study.

Semi-structured questionnaire

A semi-structured questionnaire was constructed to interview the participants, which included demographic data, details of PD, and questionnaires to assess cognition, depressive symptoms, and sleep disorders.

Demographic data

The first part included demographic variables including age, gender, and BMI.

Clinical data

The second part comprised associated comorbidities along with PD and details regarding its treatment. It included age of onset of PD (< 50 years: early-onset PD; > 60 years: late-onset PD),^[27] disease duration, disease phenotype (tremor-dominant, postural instability/gait difficulty, or mixed type),^[28] Hoehn and Yahr stage, duration of dopaminergic therapy, levodopa equivalent daily dose (LEDD),^[29] MoCA, depressive symptoms assessment using Patient Health Questionnaire-9 (PHQ-9),^[30] sleep quality using Parkinson's disease sleep scale-2 (PDSS-2; for PD patients)^[31,32] and Pittsburgh Sleep Quality Index (PSQI; for PD patients and healthy controls),^[33] excessive daytime sleepiness (EDS) using Epworth sleepiness scale (ESS),^[34,35] insomnia symptoms and severity using insomnia severity index (ISI),^[36-38] presence of RLS using IRLSSG criteria,^[22] and presence of RBD using REM Sleep Behavior Disorder Single-Question Screen (RBD1Q).^[39]

Scales used for assessment of subjective sleep quality and selected sleep disorders

Parkinson's disease sleep scale-2

PDSS-2 is a self-administered questionnaire used to assess sleep quality in PD patients.^[31] Eight components are evaluated with 15 questions: overall quality of night's sleep (question 1), sleep onset and maintenance insomnia (questions 2 and 3), nocturnal restlessness (questions 4 and 5), nocturnal psychosis (questions 6 and 7), nocturia (questions 8 and 9), nocturnal motor symptoms (questions 10–13), sleep refreshment (question 14), and daytime dozing (question 15). Each question is rated using a frequency score, ranging from 0 (never) to 4 (very often). The total PDSS-2 score ranges from 0 (no disturbance)

to 60 (maximum nocturnal disturbance). It has a sensitivity of 77.6% and specificity of 74.3%. A cut-off score of ≥ 18 differentiates poor from good sleepers.^[32]

Pittsburgh Sleep Quality Index

This 19-item, self-rated questionnaire evaluates sleep quality over past 1 month. The items are grouped into seven components, including (1) sleep duration, (2) sleep disturbance, (3) sleep latency, (4) daytime dysfunction due to sleepiness, (5) sleep efficiency, (6) overall sleep quality, and (7) sleep medication use. A score ranging from 0 to 3 is given for each component, with 3 indicating the greatest disturbance. Summing the scores of all seven components gives the global score, which ranges from 0 to 21. Higher the global score, worse the sleep quality. A global PSQI score > 5 gives a sensitivity of 89.6% and specificity of 86.5% with an internal consistency of 0.75 to differentiate good sleepers from poor sleepers.^[33]

Epworth sleepiness scale

ESS is a self-administered questionnaire that has questions asking the subject about the tendency to doze off while engaged in eight different activities. Participants need to rate each of the eight questions on a 4-point scale (0–3), with 0 = would never doze and 3 = high chance of dozing.^[34] The total ESS score ranges from 0 to 24, with a higher score suggesting high likelihood of daytime sleepiness. An ESS score > 10 defines EDS, with a sensitivity of 93.5% and specificity of 100%. We used the validated Hindi version of ESS.^[35]

Insomnia severity index (ISI)

ISI is a patient-reported measure to assess insomnia severity during past 2 weeks.^[36] It is composed of seven items that assess the severity of sleep onset (initial), sleep maintenance (middle), and early morning awakening (terminal) problems, along with satisfaction with the current sleep pattern, noticeability of impairment in quality of life attributed to the sleep problem, level of distress caused by the sleep issues, and interference with daily functioning. Each of these items is rated on a 5-point scale (0 = none; 4 = very much). Total scores range from 0 to 28. Score below 8 is considered clinically insignificant insomnia, 8–14 as mild, 15–21 as moderate, and 22–28 as severe insomnia.^[36,37] For the diagnosis of significant insomnia, a cut-off score of ≥ 10 in community and ≥ 11 in clinical cohort has a sensitivity of 86.1% and 97.2% and specificity of 87.7% and 100%, respectively.^[37] Its validated Hindi version was used (Cronbach's alpha of 0.91).^[38]

IRLSSG rating scale

All participants were screened for RLS using the IRLSSG criteria^[22] by two authors (RG and NK) experienced in diagnosis and management of RLS. RLS was diagnosed by face-to-face interview along with clinical examination. Conditions mimicking RLS were excluded.

REM Sleep Behavior Disorder Single-Question Screen

Assessment of RBD was based on a single-item screening.^[39] It has been found to have 93.8% sensitivity and 87.2% specificity

for the diagnosis of RBD in the general (idiopathic RBD and control) population.^[39] Among patients having PD, it has a sensitivity of 93% and specificity of 68%.^[40] The RBD1Q consists of a single question that could be answered “yes” or “no,” which is as follows: “Have you ever been told, or suspected yourself, that you seem to ‘act out your dreams’ while asleep (e.g., punching, flailing your arms in the air, making running movements, etc.)?”

The Hindi translation of RBD1Q was done as per the following translation procedure. The original question was translated to Hindi independently by two persons proficient in both English and Hindi. Both the translators discussed the content of their respective Hindi versions and prepared a common, third Hindi version. The third version was then back translated to English by two other translators who were well versed with both the languages. Based upon the discussion with both the back translators, sixth, common English version was developed. This was matched with the original scale to check for the consistency of the items. Wherever there was a gross discrepancy, the issue was discussed and a change was made in the third version to communicate the same meaning as the original English version. This brought the final Hindi version (version 7) ready for use. It was then applied in a small subset of individuals and they were asked to comment on the clarity and comprehensibility of the final Hindi questionnaire. After ensuring that the language was comprehensible for the study population, it was used for the collection of data in the study population.

Patient Health Questionnaire–9

PHQ-9 assesses subjects based on nine criteria for depression on a 4-point Likert's scale ranging from not at all (score 0) to nearly every day (score 3). It has a score ranging between 0 and 27. PHQ score of 0–4 shows no or minimal depression. Scores between 5 and 9, 10 and 14, 15 and 19, and > 20 represent mild, moderate, moderately severe, and severe depression, respectively. PHQ-9 score ≥ 5 has a sensitivity and specificity of 88% each for major depressive disorder.^[30] We used the Hindi version of PHQ-9 to assess depression and mood.

Statistical analysis

The analysis was done using Statistical Package for Social Sciences (SPSS) v 28.0 (IBM Corp. released 2021, IBM SPSS Statistics for Mac, Version 28.0.1.0 [142]; IBM Corp., Armonk, NY, USA). Descriptive statistics was calculated. Normality of data was tested using Shapiro–Wilk test. Numerical variables were expressed as mean \pm standard deviation for normal distribution or median with interquartile range (IQR) for skewed distribution. Categorical variables were expressed as proportions and percentages. Chi-square test was used to compare categorical variables across groups. To compare continuous variables across groups that were normally distributed, paired *t*-test and independent sample *t*-test were applied, while Mann–Whitney U test was used where distribution of numerical variables was skewed. Effect size for abnormal sleep parameters was calculated using odds

ratio. Multivariate binary logistic regression was used to find independent predictors of sleep disturbances, which included variables with $P < 0.1$ on univariate analysis. A variable with a two-tailed P value of less than 0.05 was considered statistically significant.

RESULTS

A total of 50 PD patients and 50 healthy controls were recruited in the study. The mean age was 59.12 ± 11.14 years in patients and 58.96 ± 10.62 years in the control group. While males constituted 54% of patients, they constituted 56% of controls. While the mean BMI (in kg/m^2) in patients was 23.3 ± 3.1 , it was 24.3 ± 3.0 in controls. No comorbidity was reported by 31 (62%) patients and 34 (68%) controls. Fourteen patients (28%) and 12 (24%) controls had hypertension and/or diabetes, respectively. Mean \pm SD for MoCA scale score was 26.9 ± 2.0 and 27.5 ± 2.3 in patients and controls, respectively.

Group with PD

The mean age of onset of symptoms in PD patients was 53.9 ± 10.7 years. Early-onset PD comprised 30% patients. Tremor-predominant subtype was seen in 46% patients. The median (IQR) disease duration was 6 years (3–6.2). The median (IQR) Unified Parkinson's Disease Rating Scale UPDRS-III score was 33 (12.7–44) and median (IQR) LEDD was 500 mg (375–625). More than two-thirds (68%) of the patients had Hoehn and Yahr stage of ≤ 2 of PD.

More than two-thirds (72%) of the PD patients reported poor sleep quality (PDSS-2 ≥ 15 , PSQI > 5). While 60% patients had insomnia (ISI ≥ 10), 58% reported RBD, half of them had EDS (ESS > 10), and more than one third (36%) reported RLS [Table 1]. Depressive symptoms (PHQ-9 ≥ 5) were reported by 70% patients.

Comparison of PD patients with and without poor sleep

Comparison of PD patients with and without poor sleep quality showed that both groups were comparable with regards to demographic variables, comorbidities, and variables related to PD and its treatment, except for depressive symptoms ($P < 0.001$). Although patients with poor sleep quality had a relatively higher median Hoehn and Yahr stage, it failed to show a significant association on multivariate logistic regression ($P = 0.15$). Similarly, majority of the demographic and clinical variables were comparable in those with and without insomnia, EDS, RBD, and RLS. While presence of depressive symptoms showed a significant association with EDS ($P = 0.008$) and RBD ($P < 0.001$), insomnia was significantly associated with depression ($P = 0.001$) and LEDD ($P = 0.02$) [Supplementary Table 1].

Comparison of sleep disorders between PD and control groups

While 44 (88%) PD patients reported one or more sleep disorders, 14 (28%) controls reported them. Table 1 shows a significantly higher prevalence of poor sleep quality ($P < 0.001$), EDS ($P < 0.001$), insomnia ($P < 0.001$),

RLS ($P = 0.002$), and RBD ($P < 0.001$) in PD patients compared to controls. While most of the demographic and clinical factors were comparable between PD patients and healthy controls having sleep disorders, presence of depressive symptoms was significantly associated with poor sleep quality ($P = 0.002$) and RBD ($P = 0.01$) in PD patients [Table 2].

DISCUSSION

This study showed that during COVID-19 pandemic, prevalence of sleep disturbances (poor sleep quality, EDS, insomnia, RLS, and RBD) was higher among PD patients compared to age, gender, and BMI-matched healthy controls. The prevalence of EDS, RLS, and RBD was higher compared to that reported in Indian studies conducted during pre-COVID period. Presence of depressive symptoms in PD patients was significantly associated with poor sleep quality, EDS, insomnia, and RBD. When compared to controls, presence of depressive symptoms was significantly associated with poor sleep quality and RBD in PD patients.

Worldwide, sleep disturbances are reported in up to 90% PD patients, with insomnia reported in up to 80%, EDS in up to 20%–60%, RBD in up to 46%, and RLS in up to 22% of PD patients.^[9,41] On the other hand, Indian studies in the pre-COVID-19 period have reported lower prevalence, for example, poor sleep quality in 16%–87%,^[12,13,21] insomnia in 30%–77%,^[12,15,16] EDS in 10%–30%,^[13,14,17] RBD in 19%–25%,^[15,20] and RLS in 8%–15% of PD patients.^[15,18,19] While the prevalence of poor sleep quality and insomnia in this study was comparable to that reported in the pre-COVID Indian studies, prevalence of EDS, RBD, and RLS was greater. Variation from the Western literature could be related to differences in sleep-wake pattern, prevalence of sleep disorders in the general Indian population, and racial differences in the quality of care to the patients with PD, while the difference from Indian studies could be ascribed to stress, limited opportunities of consultations, and altered sleep-wake patterns, besides the other factors discussed below.^[10,11]

EDS and RBD in PD have been found to be associated with non-tremor-dominant subtype of PD, motor fluctuations, longer disease duration, advanced disease stage with higher UPDRS-III score, higher LEDD, presence of depressive symptoms, and cognitive impairment.^[41] In addition to the nigrostriatal degeneration, progression in PD affects several brainstem areas involved in regulation of sleep and wakefulness, including the pedunculopontine nucleus, locus coeruleus, nucleus magnocellularis, and tegmental area, thereby producing sleep disorders including EDS, RBD, and RLS as well as depression.^[42] A higher prevalence of EDS in the present study may additionally be related to a longer disease duration (72 vs. 44.8 months),^[14] less number of tremor-dominant PD subtype (46% vs. 69%),^[13] a higher UPDRS-III motor score (33 vs. 25.3),^[17] and a higher average LEDD (500 vs. 367.5 mg)^[14] compared to those reported in previous Indian studies. A higher prevalence of RBD in the

Table 1: Comparison of prevalence of sleep disorders and depressive symptoms between cases having PD and healthy controls

	Sleep scales	Case (n = 50)	Control (n = 50)	Statistical test	P value*	Odds ratio (95% CI)
1	Poor sleep quality Global PSQI>5 ^a , n (%)	36 (72)	9 (18)	$\chi^2 = 29.45$	<0.001	11.7 (4.5–30.3)
2	EDS ESS>10 ^b , n (%)	25 (50)	2 (4)	$\chi^2 = 26.83$	<0.001	24 (5.2–109.6)
3	Insomnia symptoms ISI≥10 ^c , n (%)	30 (60)	1 (2)	$\chi^2 = 39.32$	<0.001	73.5 (9.3–576.2)
4	RLS, n (%)	18 (36)	5 (10)	$\chi^2 = 9.54$	0.002	5.1 (1.7–15.1)
5	RBD, n (%)	29 (58)	4 (8)	$\chi^2 = 28.27$	<0.001	15.9 (4.9–50.9)
6	Depressive symptoms PHQ-9≥5 ^d , n (%)	35 (70)	3 (6)	$\chi^2 = 43.46$	<0.001	36.5 (9.8–136.1)

CI = confidence interval, EDS = excessive daytime sleepiness, ESS = Epworth sleepiness scale, ISI = insomnia severity index, PD = Parkinson's disease, PHQ-9 = Patient Health Questionnaire-9, PSQI = Pittsburgh Sleep Quality Index, RBD = rapid eye movement sleep behavior disorder, RLS = restless legs syndrome. χ^2 = Pearson Chi square. *Chi-square test. ^aPSQI≤5 – good sleep, PSQI>5 – poor sleep; ^bESS≤10 – no EDS, ESS>10 – probable or definite EDS; ^cISI<10 (controls) and<11 (PD patients) – no or subthreshold insomnia, ISI≥10 (controls) and≥11 (PD patients) – significant insomnia; ^dPHQ-9<5 – no or minimal depression, PHQ-9≥5 – mild, moderate, or severe depression

Table 2: Factors associated with poor sleep quality, restless legs syndrome, and rapid eye movement behavior disorder in PD and control groups

S. no.	Variables [#]	Disease present	Disease absent	P value
A	Poor sleep quality (global PSQI>5)	PD (n = 36)	Healthy controls (n = 9)	
1	Demographic variables			
	Age, median (IQR)	60.5 (54–66.7)	65 (58–68)	0.29
	Female gender, n (%)	19 (52.8%)	4 (44.4%)	0.72
	BMI, median (IQR)	22.9 (21.1–26.4)	25.3 (20.6–27.9)	0.70
2	Clinical variables			
	Associated HT and/or DM, n (%)	12 (33.3%)	1 (11.1%)	0.24
	MoCA score, median (IQR)	26.5 (25–28)	28 (25–29.5)	0.47
	Depressive symptoms (PHQ-9≥5), n (%)	32 (88.9%)	3 (33.3%)	0.002
B	Restless legs syndrome	PD (n = 18)	Healthy controls (n = 5)	
1	Demographic variables			
	Age, median (IQR)	62 (55.5–73.7)	55 (53–62)	0.21
	Female gender, n (%)	8 (44.4%)	2 (40%)	1.00
	BMI, median (IQR)	23.9 (20.9–27.9)	27.7 (22.4–28.7)	0.32
2	Clinical variables			
	Associated HT and/or DM, n (%)	7 (38.9%)	0 (0%)	-
	MoCA score, median (IQR)	26.5 (25–28)	25 (24–30)	0.62
	Depressive symptoms (PHQ-9≥5), n (%)	15 (83.3%)	2 (40%)	0.08
C	RBD	PD (n = 29)	Healthy controls (n = 4)	
1	Demographic variables			
	Age, median (IQR)	61 (54.5–69)	66 (47.2–78.7)	0.50
	Female gender, n (%)	14 (48.3%)	3 (75%)	0.60
	BMI, median (IQR)	23.4 (21.3–26.4)	23.1 (20.7–27.1)	0.74
2	Clinical variables			
	Associated HT and/or DM, n (%)	8 (27.6%)	0 (0%)	-
	MoCA score, median (IQR)	27 (25.5–29.5)	27.5 (24.2–30)	0.88
	Depressive symptoms (PHQ-9≥5), n (%)	26 (89.7%)	1 (25%)	0.01

BMI = body mass index, DM = diabetes mellitus, EDS = excessive daytime sleepiness, ESS = Epworth sleepiness scale, HT = hypertension, IQR = interquartile range, ISI = insomnia severity index, MoCA = Montreal Cognitive Assessment, PD = Parkinson's disease, PSQI = Pittsburgh Sleep Quality Index, PHQ-9 = Patient Health Questionnaire-9, RBD = rapid eye movement sleep behavior disorder. [#]EDS and insomnia symptoms are not presented in the table as only two and a single healthy control reported these symptoms, respectively

present study might have been contributed by a higher mean age of PD patients (59.12 vs. 57.43 years) and a longer disease duration (72 vs. 66 months) in our cohort.^[15]

The prevalence of RLS in this study was higher compared to the proportion reported in Indian studies that were conducted during the pre-COVID-19 times (36% vs. 8%–15%).^[15,18,19]

RLS in PD was reported to be associated with a higher age, female gender, presence of motor fluctuations, depression, and cognitive impairment.^[41] Compared to earlier studies, in the present study, mean age of the study participants was greater (59.12 vs. 57.4 vs. 57.8 vs. 56.7 years), duration of disease was longer (72 vs. 66 vs. 61.2 vs. 55.2 months), and the proportion of female patients was greater (46% vs. 22% vs. 10% vs. 34.5%).^[15,18,19] These factors might have contributed to the higher prevalence of RLS in this study, besides the factors associated with COVID-19 pandemic.^[41]

While majority of the demographic and clinical factors failed to show any significant association with sleep disturbances, presence of depressive symptoms was significantly associated with poor sleep quality, EDS, insomnia, and RBD. Although we did not compare the motor and non-motor features in PD patients with their pre-pandemic status in the present study, previous studies from our group have shown that motor (tremor, stiffness, and slowness) as well as non-motor features (depressive and anxiety symptoms) had worsened during COVID-19 pandemic; however, in the absence of clinical examination, there is a possibility that disturbance of mood, sleep, and motor symptoms could have been overestimated.^[24,25] Cohort used in the present study was also part of previous studies.^[24,25] Depressive symptoms have been reported to be significantly associated with sleep disorders including insomnia, EDS, RBD, and RLS in the past.^[41,42] Moreover, sleep disorders often act as a predictor of depression in PD.^[41,43] Further, dopamine dysfunction in PD, that is, lack of compensatory dopamine rise following sleep loss in PD patients, precipitates and/or worsens depressive symptoms.^[43] These factors suggest that COVID-19 pandemic may have played a role in the occurrence of EDS, RBD, and RLS in the study group. As the disease progresses, this lack of compensatory dopamine rise becomes more evident. However, we did not find a significant association of Hoehn and Yahr stage with the assessed sleep parameters on multivariate analysis in this study. Worsening of motor problems such as rigidity, limb dystonia and tremor and non-motor issues including anxiety and frequent urination might have also contributed to the sleep disturbances in PD.^[9,41]

Like any other scientific investigation, the present study has some methodological limitations. First, small sample size is a major limitation of this study. Second, risk of recall bias while the participants answered the questionnaires could not be excluded. Third, apart from the LEDD, we did not look into the details of medications and their relationship with sleep disturbances. Fourth, we did not assess motor and non-motor fluctuations which might have also affected sleep in PD patients. Fifth, we did not assess nocturia, obstructive sleep apnea, anxiety, and the quality of life. Sixth, lack of polysomnography limits our ability to compare data of the present study with that from other studies which used polysomnography. Seventh, to understand the effect of COVID-19 pandemic on sleep among PD patients, a follow-up study would have been better. However, this pandemic was

an unpredictable situation, and hence, the results of the study conducted during the pandemic were compared to those from pre-pandemic studies. However, our study coincided with the prolonged repeated lockdowns during the ongoing COVID-19 pandemic and presents comparative data with those of healthy age, gender, and BMI-matched controls.

CONCLUSION

Prevalence of sleep disorders increased in PD patients during the COVID-19 pandemic. Of the different sleep disorders, a higher prevalence of EDS, RBD, and RLS was observed compared to that reported in studies during the pre-COVID-19 times. Presence of depressive symptoms was a significant correlate of presence of sleep disorders in PD patients.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Authors contributions

Dr. Ishita Desai: writing the first draft; Dr. Ravi Gupta: conception, design, review, and critique; Dr. Mritunjai Kumar: review and critique; Dr. Ashutosh Tiwari: review and critique; Dr. Niraj Kumar: conception, design, writing the first draft, review, and critique.

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Conflicts of interest

There are no conflicts of interest.

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Supplementary Table 1: Regression analysis for the independent predictors of poor sleep quality, excessive daytime somnolence, insomnia symptoms, RBD, and RLS among patients having PD

S. no.	Variable [#]	Disease present	Disease absent	P value*	Adj. P** (CI)
A	Poor sleep quality	PDSS-2 ≥18 (n = 36)	PDSS-2 <18 (n = 14)		
1	Demographic variables				
	Age (years), median (IQR)	60.5 (54–67.7)	57 (44.2–64.2)	0.26	-
	Female gender, n (%)	19 (52.8%)	4 (28.6%)	0.20	-
	BMI, median (IQR)	23.2 (20.9–26.3)	22.4 (20.8–24)	0.40	-
2	Clinical variables				
	Associated HT and/or DM, n (%)	12 (33.3%)	2 (14.3%)	0.29	-
	Early-onset PD, n (%)	10 (27.8%)	5 (35.7%)	0.58	-
	Disease duration (years), median (IQR)	6 (4–6.7)	4.5 (2.8–6.2)	0.27	-
	Tremor-dominant PD, n (%)	15 (41.7%)	8 (57.1%)	0.32	-
	Hoehn and Yahr stage, median (IQR)	2 (2–3)	2 (1.75–2)	0.02	0.15 (0.69–9.29)
	LEDD (in mg), median (IQR)	500 (425–866.2)	462.5 (225–527.5)	0.11	-
	MoCA score, median (IQR)	26 (25–28)	27.5 (25–29)	0.51	-
	Depressive symptoms (PHQ-9≥5), n (%)	32 (88.9%)	3 (21.4%)	<0.001	<0.001 (0.01–0.22)
B	Excessive daytime sleepiness	ESS>10 (n = 25)	ESS≤10 (n = 25)		
1	Demographic variables				
	Age (years), median (IQR)	62 (53–73)	58 (48–64.5)	0.18	-
	Female gender, n (%)	13 (52%)	10 (40%)	0.39	-
	BMI, median (IQR)	23.1 (21–26.6)	22.6 (20.6–24.1)	0.33	-
2	Clinical variables				
	Associated HT and/or DM, n (%)	9 (36%)	5 (20%)	0.20	-
	Early-onset PD, n (%)	8 (32%)	9 (36%)	0.76	-
	Disease duration (years), median (IQR)	6 (4–9)	5 (3–6)	0.29	-
	Tremor dominant PD, n (%)	12 (48%)	11 (44%)	0.77	-
	Hoehn and Yahr stage, median (IQR)	2 (2–3.5)	2 (1.5–2)	0.05	0.19 (0.78–3.49)
	LEDD (in mg), median (IQR)	500 (462.5–827.5)	500 (337.5–500)	0.10	0.36 (0.99–1.0)
	MoCA score, median (IQR)	27 (25–28)	27 (25–29.5)	0.71	-
	Depressive symptoms (PHQ-9≥5), n (%)	23 (92%)	12 (48%)	<0.001	0.008 (0.01–0.56)
C	Insomnia	ISI≥11 (n = 30)	ISI<11 (n = 20)		
1	Demographic variables				
	Age (years), median (IQR)	59.5 (53.5–64.5)	61 (46.5–67)	0.18	-
	Female gender, n (%)	15 (50%)	8 (40%)	0.48	-
	BMI, median (IQR)	22.9 (20.9–26.4)	22.8 (20.9–24.2)	0.33	-
2	Clinical variables				
	Associated HT and/or DM, n (%)	10 (33.3%)	4 (20%)	0.30	-
	Early-onset PD, n (%)	11 (36.7%)	6 (30%)	0.62	-
	Disease duration (years), median (IQR)	6 (4–8.2)	4.5 (3–6)	0.29	-
	Tremor-dominant PD, n (%)	12 (40%)	11 (55%)	0.29	-
	Hoehn and Yahr stage, median (IQR)	2 (2–3.2)	2 (1.13–2)	0.05	0.21 (0.57–12.23)
	LEDD (in mg), median (IQR)	500 (481.2–910)	462.5 (75–500)	0.10	0.02 (1.0–1.007)
	MoCA score, median (IQR)	26 (25–28)	27.5 (25.2–29)	0.71	-
	Depressive symptoms (PHQ-9≥5), n (%)	29 (96.7%)	6 (30%)	<0.001	0.001 (0.0–0.14)
D	RBD	RBD present (n = 29)	RBD absent (n = 21)		
1	Demographic variables				
	Age (years), median (IQR)	61 (54.5–69)	57 (45–65)	0.14	-
	Female gender, n (%)	14 (48.3%)	9 (42.9%)	0.70	-
	BMI, median (IQR)	23.4 (21.3–26.4)	21.4 (20.3–24.1)	0.12	-
	Associated HT and/or DM, n (%)	8 (27.6%)	6 (28.6%)	0.93	-
2	PD-related variables				
	Early-onset PD, n (%)	8 (27.6%)	9 (42.9%)	0.26	-
	Disease duration (years), median (IQR)	6 (3–7.5)	5 (3–6)	0.67	-
	Tremor-dominant PD, n (%)	11 (37.9%)	12 (57.1%)	0.17	-
	Hoehn and Yahr stage, median (IQR)	2 (2–3)	2 (2–2)	0.13	-

Contd...

Supplementary Table 1: Contd...

S. no.	Variable [#]	Disease present	Disease absent	P value*	Adj. P** (CI)
	LEDD (in mg), median (IQR)	500 (425–827.5)	500 (187.5–555)	0.22	-
	MoCA score, median (IQR)	27 (25.5–29.5)	27 (24–28)	0.14	-
	Depressive symptoms (PHQ-9 \geq 5), n (%)	26 (89.7%)	9 (42.9%)	<0.001	-
E	RLS	RLS present (n = 18)	RLS absent (n = 32)		
1	Demographic variables				
	Age (years), median (IQR)	62 (55.5–73.7)	58.5 (47.2–64)	0.11	-
	Female gender, n (%)	8 (44.4%)	15 (46.9%)	0.86	-
	BMI, median (IQR)	23.9 (20.9–27.9)	22.5 (20.9–25.1)	0.22	-
	Associated HT and/or DM, n (%)	7 (38.9%)	7 (21.9%)	0.19	-
2	PD-related variables				
	Early-onset PD, n (%)	5 (27.8%)	12 (37.5%)	0.48	-
	Disease duration (years), median (IQR)	5.5 (3–7.7)	6 (3–6)	0.77	-
	Tremor-dominant PD, n (%)	7 (38.9%)	16 (50%)	0.44	-
	Hoehn and Yahr stage, median (IQR)	2.2 (1.8–3)	2 (2–2)	0.24	-
	LEDD (in mg), median (IQR)	500 (281.2–788.7)	500 (387.5–582.5)	0.74	-
	MoCA score, median (IQR)	26.5 (25–28)	27 (25–29)	0.98	-
	Depressive symptoms (PHQ-9 \geq 5), n (%)	15 (83.3%)	20 (62.5%)	0.12	-

Adj. = adjusted, BMI = body mass index, DM = diabetes mellitus, ESS = Epworth sleepiness scale, HT = hypertension, IQR = interquartile range, ISI = insomnia severity index, LEDD = levodopa equivalent daily dose, MoCA = Montreal Cognitive Assessment, PD = Parkinson's disease, PDSS-2 = Parkinson's disease sleep scale-2, PHQ-9 = Patient Health Questionnaire-9, RBD = rapid eye movement sleep behavior disorder, RLS = restless legs syndrome. *Univariate analysis. **Adj. for baseline variables with $P < 0.1$ on univariate analysis