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Original Article

Manifestations of different sleep disorders in patients with vascular parkinsonism and their impact on prognosis

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Abstract: Objective: To investigate the clinical manifestations of various sleep disorders in patients with vascular parkinsonism (VP) and analyze their impact on disease prognosis. Methods: A retrospective study was conducted on 125 VP patients. Sleep disorders were assessed using the Insomnia Severity Index, Pittsburgh Sleep Quality Index, Epworth Sleepiness Scale, Chalder Fatigue Scale, Hamilton Anxiety Rating Scale, Hamilton Depression Rating Scale, Restless Legs Syndrome Severity Self-Rating Scale, REM sleep behavior disorder (RBD) Severity Questionnaire, and Idiopathic Hypersomnia Questionnaire. VP severity was evaluated using all four sections of the Unified Parkinson's Disease Rating Scale (UPDRS). Logistic regression analysis was employed to evaluate the independent impact of different sleep disorders on adverse prognosis in VP patients. Results: 64.0% of patients had at least one sleep disorder, with insomnia (44.0%), RBD (37.6%), and restless legs syndrome (28.0%) being the most common. Patients with RBD had significantly higher UPDRS Part I and Part IV scores ($P < 0.01$). Multivariate logistic regression analysis revealed that insomnia (OR = 4.489, 95% CI: 1.903-10.589) and RBD (OR = 4.318, 95% CI: 1.814-10.280) were independent risk factors for adverse prognosis within one year. Conclusions: VP patients have a high incidence of various sleep disorders, which are closely associated with specific motor and non-motor symptoms as well as disease prognosis. Among these, RBD and insomnia serve as important clinical indicators for predicting poor prognosis in VP patients. Early identification and intervention of these sleep disorders may help delay disease progression and improve patients' quality of life.

Keywords: Vascular parkinsonism, sleep disorders, rapid eye movement sleep behavior disorder, restless legs syndrome, insomnia, prognosis, scale assessment

Introduction

Sleep occupies about one-third of a person's lifespan and is a crucial physiological process for maintaining homeostasis, cognitive function, and emotional health [1, 2]. In recent years, the development of sleep medicine has greatly deepened people's understanding of sleep disorders - its scope is no longer limited to the narrow concept of "insomnia", but has been recognized as a complex disease spectrum encompassing seven major categories and hundreds of diseases, including insomnia disorders, sleep-related breathing disorders, central hypersomnia disorders, circadian rhythm sleep-wake disorders, sleep-related motor disorders, and parasomnias [3]. It is worth noting that specific sleep disorders such as rapid eye movement sleep behavior disorder (RBD), restless legs syndrome (RLS), and obstructive sleep apnea syndrome (OSAS) are closely related to neurological diseases, and this association is increasingly being recognized [3-6].

Parkinson's syndrome is a group of clinical syndromes characterized by core motor symptoms such as bradykinesia, muscle rigidity, resting tremor, and abnormal posture and gait, with diverse etiologies [7-9]. In addition to the above typical motor manifestations, patients often have a variety of non-motor symptoms, among which sleep disorders are the most prominent and prevalent type [10]. Extensive evidence indicates that sleep disorders in Parkinson's disease (PD) patients are not merely incidental; specific types, such as rapid eye movement sleep behavior disorder (RBD), have been considered valuable biomarkers for the prodromal

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phase of α-synucleinopathy-related neurodegenerative diseases (e.g., PD, Lewy body dementia) [11]. Notably, RBD can occur more than a decade before the onset of typical motor symptoms [6-10].

However, most existing research focuses only on idiopathic PD [11, 12]. In contrast, vascular parkinsonism (VP), a secondary parkinsonism syndrome caused by cerebrovascular lesions, differs from PD in clinical presentation, underlying pathophysiological mechanisms, and treatment response, yet it has received far less attention [13, 14]. To date, systematic studies on the disease spectrum, clinical characteristics, and prognostic significance of sleep disorders in VP patients remain severely lacking [21, 22]. Given that VP patients often have multiple cerebrovascular risk factors and extensive white matter lesions, a key question arises: Do their sleep disorders present a unique pattern of manifestation [23, 24]? Are these sleep disorders directly related to the location of cerebrovascular lesions, or do they reflect broader abnormalities in brain network function [25, 26]? Furthermore, how do different types of sleep disorders affect motor function, non-motor symptom load, and long-term prognosis in VP patients? Answering these questions is crucial for a comprehensive understanding of VP, early identification of high-risk groups, and guidance for individualized treatment interventions [15, 16].

This study aims to fill this gap. A retrospective analysis was conducted on a cohort of VP patients using standardized assessment scales. The prevalence of multiple sleep disorders, including insomnia, RBD, RLS, and OSAS, was systematically evaluated, and their association with motor severity, non-motor symptom load, and short-term clinical prognosis was further explored. This study constructed a practical integrated "sleep-motor" assessment framework based on clinically easy-to-use scales, exploring new intervention targets to improve the prognosis of VP patients.

Materials and methods

Study subjects

This study retrospectively collected clinical data from 125 VP patients admitted the Department of Neurology at Hebei Medical University Third Hospital between June 2019 and December 2023. This study was approved by the Ethics Committee of the Hebei Medical University Third Hospital. Due to the retrospective nature, informed consent was waived, and all data were anonymized to strictly protect patient privacy. All procedures involving human subjects complied with the relevant provisions of the Declaration of Helsinki (2013 revised edition).

Inclusion and exclusion criteria

Inclusion Criteria: diagnosed with VP according to the internationally recognized criteria [17]; age ≥ 50 years; disease duration ≥ 6 months; completion of a full set of standardized scales for Parkinson's symptoms and sleep symptoms at Hebei Medical University Third Hospital; and availability of complete clinical medical records, neuroimaging data, and follow-up records.

Exclusion Criteria: multiple system atrophy, Lewy body dementia, or other neurodegenerative diseases; severe systemic diseases (such as advanced liver or kidney failure, active malignant tumors, acute cardiovascular or cerebrovascular events) that could significantly affect symptom assessment or prognosis; inability to complete the assessment due to severe cognitive or mental impairment, or the caregiver cannot provide reliable alternative information; lack of core clinical data required for symptom grading or sleep disorder classification; participation in other sleep disorder or PD-related interventional trials, which may lead to bias in the study results (**Figure 1**).

Diagnostic criteria

Diagnostic Criteria for VP: According to international standards, all of the following criteria must be met simultaneously: Presence of parkinsonian-like motor dysfunction, primarily manifested as gait abnormalities (such as festinating gait, freezing gait) and bilateral symmetrical rigidity, with tremor being relatively rare; a clear history of cerebrovascular disease (cerebral infarction/cerebral hemorrhage), and neuroimaging examinations (MRI/CT scan) showing corresponding vascular lesions in the cerebral hemispheres, basal ganglia, or brainstem; a clear temporal correlation between Parkinsonian symptoms and cerebrovascular events (usually with acute or subacute onset); exclu-

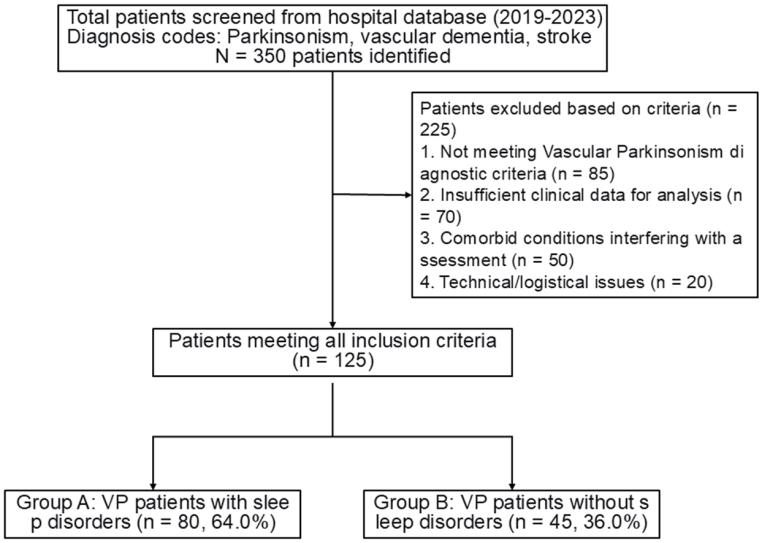

Figure 1. Patient selection flowchart. Abbreviations: VP, vascular parkinsonism.

sion of other types such as idiopathic PD and drug-induced Parkinson's syndrome.

Diagnostic and Classification Criteria for Sleep Disorders: Based on the International Classification of Sleep Disorders [18], a strategy of "primarily using scales for initial screening, supplemented by polysomnography (PSG) verification" is adopted for diagnosis and classification. Specifically, insomnia was defined as Insomnia Severity Index (ISI) score ≥ 8, and Pittsburgh Sleep Quality Index (PSQI) total score ≥ 7.

RBD was defined as positive scores on the RBD Severity Questionnaire. For patients with typical dream-enactment behaviors, diagnosis was established based on rapid eye movement sleep without atonia on PSG when performed. For those without PSG examination, clinical diagnosis was made according to typical clinical manifestations combined with questionnaire findings.

RLS was diagnosed according to the International RLS Study Group, and its severity was assessed using the RLS Severity Self-Rating Scale.

OSAS was determined primarily by PSG results, with an apnea-hypopnea index ≥ 5 events/hour, combined with the Epworth Sleepiness Scale (ESS) to assess daytime sleepiness. Narcolepsy, periodic limb movement disorder, etc., were diagnosed based on relevant scales, clinical symptoms, and PSG results.

PSG was only performed on patients whose medical history and scale screening suggested possible RBD or OSAS and was used to confirm the diagnosis. Suspected RBD was defined as having at least one of the following clinical features: the patient or bed partner reports dream enactment behavior (such as punching, kicking, shouting, etc. during sleep), or a positive RBD Severity Questionnaire screening (score ≥ 18 points). Suspected OSAS was defined as an ESS score ≥ 10 points, accompanied by at least one of the following symptoms: habitual snoring, witnessed apnea, or morning headache. Other types of sleep disorders were mainly diagnosed based on relevant scales and clinical assessment, and PSG was not mandatory.

Data collection

Baseline Characteristics: Demographic information, cerebrovascular risk factors, stroke history (type, location, and onset time), VP course, medication use (including anti-parkinsonian drugs, sedatives, and hypnotics), and neuroimaging features were extracted from the electronic medical record system. The Fazekas scale was used to assess the severity of white matter hyperintensities.

Motor and non-motor symptom assessment: A comprehensive quantitative assessment of Parkinson's-like symptoms was conducted using all four parts of the Unified Parkinson's Disease Rating Scale (UPDRS): Part I (mentation, behavior, and emotional), Part II (activities of daily living), Part III (motor function examination), and Part IV (treatment complications). All assessments were conducted by neurologists with standardized training.

Sleep and Mood-Related Assessments: A series of reliable and valid scales completed by

patients were collected, including: Insomnia Severity Index (ISI), Pittsburgh Sleep Quality Index (PSQI), Epworth Sleepiness Scale (ESS), Chalder Fatigue Scale, Hamilton Anxiety Rating Scale (HAMA), Hamilton Depression Rating Scale (HAMD), Restless Legs Syndrome Severity Self-Rating Scale, REM sleep behavior disorder (RBD) Severity Questionnaire, and Idiopathic Hypersomnia Questionnaire.

Outcome Assessment: Following baseline assessment, prognostic data were collected from patients over 6-24 months through medical record review and telephone follow-up. For ease of analysis, adverse outcomes were operationally defined as meeting any of the following criteria: ① Disease progression: UPDRS Part III (Motor) score increased by ≥ 10 points from baseline; ② Significant decline in quality of life: Parkinson's Disease Questionnaire-39 (PDQ-39) total score worsened by ≥ 10% from baseline. In addition, events such as falls and readmissions were recorded.

The concentration of α-synuclein in cerebrospinal fluid (CSF) was detected using an enzyme-linked immunosorbent assay (ELISA) kit (catalog number 277-FL) from Fujirebio, Japan. The intra-assay coefficient of variation (CV) was 4.2%, and the inter-assay CV was 7.8%. The concentrations of interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and C-reactive protein (CRP) were detected using an ELISA kit from R&D Systems, USA. The CV for IL-6 was 3.5%, and the inter-assay CV was 6.2%; for TNF-α, the CV was 4.1%, and the inter-assay CV was 7.3%; and for CRP, the CV was 2.9%, and the inter-assay CV was 5.6%. All assays were performed strictly according to the kit instructions.

The follow-up period was 6-24 months, with a median follow-up of 15.5 months (interquartile range: 10.2-20.8 months). To assess the impact of different follow-up durations on outcome determination, a sensitivity analysis was conducted.

Quality control

All healthcare personnel involved in this study received standardized training and passed competency assessments regarding the study protocol and standardized administration of scales. The diagnosis of VP was independently confirmed by at least two neurologists. The classification of sleep disorders was verified by a neurologist specializing in sleep medicine. An independent data administrator was appointed to perform dual data entry and cross-verification, ensuring data completeness and accuracy. All PSG and sleep monitoring equipment used during the study were regularly calibrated.

Statistical analysis

Data analysis was performed using SPSS 26.0 software. Quantitative data were expressed as mean ± standard deviation (Mean ± SD), and comparisons between groups were performed using one-way ANOVA or independent samples t-tests, as appropriate. Categorical variables were expressed as frequency (%), and comparisons between groups were performed using the χ^2 test. Multivariate logistic regression analysis was conducted with adverse outcome (yes/no) as the dependent variable and age, disease duration, type of sleep disorder (e.g., RBD, insomnia, RLS), and baseline UPDRS total score as independent variables. Odds ratios (ORs) and their 95% confidence intervals (95% CIs) were calculated. Two-sided $P < 0.05$ was considered statistically significant.

For multiple comparisons, the Benjamini-Hochberg false discovery rate method was applied to adjust *P* values, and Bonferroni correction was also used. For one-way ANOVA, only the overall F-test results were reported; no post-hoc pairwise comparisons were performed, so no adjustment for multiple comparisons was applied. A two-sided adjusted $P < 0.05$ was considered statistically significant for these analyses.

Results

Distribution of sleep disorders in VP patients

Sleep disorder screening in enrolled VP patients revealed significant differences in the prevalence of various sleep disorders (**Figure 2**). Insomnia was the most common, affecting 55 patients (44.0%), followed by RBD, affecting 47 patients (37.6%), RLS, affecting 35 patients (28.0%), OSAS, affecting 28 patients (22.4%), and PLM, affecting 22 patients (17.6%). Overall, 80 patients (64.0%) had at least one sleep disorder (**Table 1**).

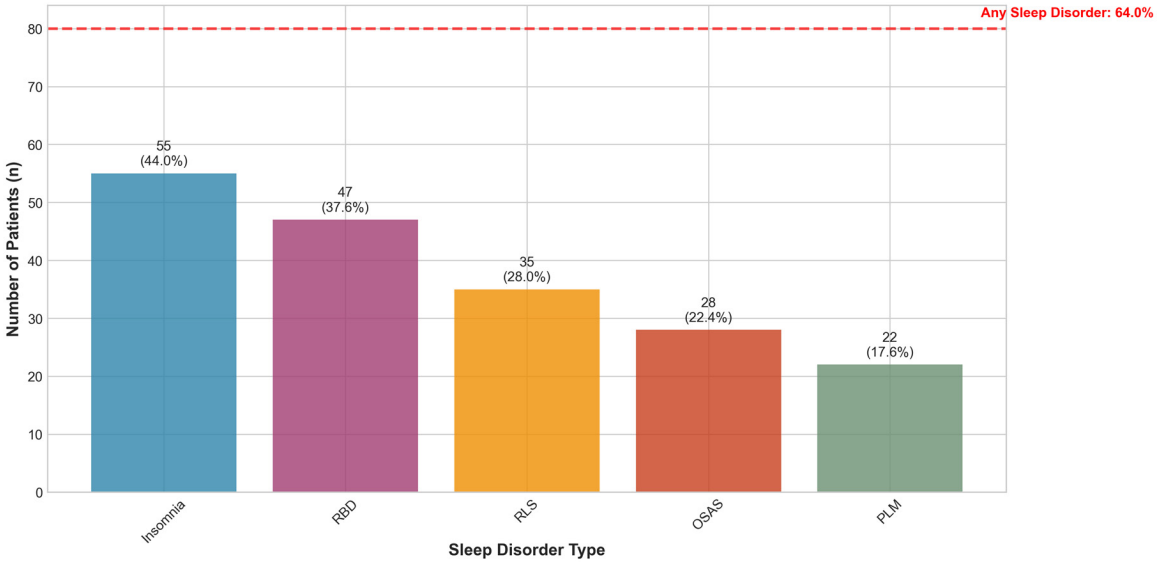

Figure 2. Prevalence of different sleep disorders in VP patients. Abbreviations: RBD, REM sleep behavior disorder; RLS, restless legs syndrome; OSAS, obstructive sleep apnea syndrome; PLM, periodic limb movement disorder.

Association between sleep disorders and clinical symptoms

The univariate comparison results of scores in each domain of the UPDRS are shown in **Figure 3**. Patients with positive RBD scores had significantly higher scores in UPDRS Part I than those with negative RBD scores (6.89 ± 2.62 vs. 5.29 ± 3.70, t = 2.818, P = 0.006; **Figure 3A**), and also significantly higher scores in UPDRS Part IV (7.79 ± 3.45 vs. 5.91 ± 4.02, t = 2.767, P = 0.007; **Figure 3B**). There was no significant difference in Part II scores between RLS-positive and RLS-negative patients (21.03 ± 11.12 vs. 18.63 ± 8.82, t = 1.142, P = 0.259; **Figure 3C**). After stratifying patients according to sleep disorder subtypes (**Figure 3D**), significant differences were found in the UPDRS Part III scores among the groups (ANOVA F = 5.728, P = 0.001). The subgroup with RBD and insomnia had the highest score (37.59 ± 11.59), followed by the RBD-only group (35.44 ± 11.33), the insomnia-only group (34.88 ± 11.38), and the group without sleep disorder (26.20 ± 14.59). The results of univariate association analysis between each sleep disorder and potential risk factors are summarized in **Table 2**. To further investigate the different roles of CRP in insomnia and RBD, we performed a multivariate logistic regression analysis after adjusting for age, sex, UPDRS-III motor score, Fazekas score, and levodopa equivalent daily dose (LEDD). After adjustment, CRP remained significantly associated with insomnia (OR = 1.354, 95% CI 1.153-1.589, P < 0.001) and RBD (OR = 1.238, 95% CI 1.063-1.442, P = 0.006) (Table S1).

Impact of sleep disorders on prognosis

Sensitivity analysis showed that including follow-up duration as a covariate in the multivariate model did not alter the primary conclusions. All 125 patients (100%) completed the follow-up, with a loss-to-follow-up rate of 0%. Kaplan-Meier analysis revealed that during the follow-up period, the cumulative incidence of adverse outcomes (defined as disease progression or significant decline in quality of life) was significantly higher in patients with positive RBD than in those with negative RBD (log-rank test χ^2 = 4.593, P = 0.032; **Figure 4A**).

To further evaluate the independent predictive value of sleep disorders, we constructed two multivariate logistic regression models. In the core clinical model, adjusted only for age, UPDRS Part III score, insomnia, RBD, and RLS, both insomnia (OR = 4.489, 95% CI 1.903-10.589, P = 0.001) and RBD (OR = 4.318, 95% CI 1.814-10.280, P = 0.001) were both significant independent predictors of adverse outcomes (Table S2). However, after further adjusting for Fazekas score, Levodopa Equivalent Daily Dose (LEDD), stroke location, and four biomarkers (CSF α-synuclein, IL-6, TNF-α, CRP)

Table 1. Baseline characteristics of the study population

Variable	Total (n = 125)	Sleep Disorder Group (n = 80)	No Sleep Disorder Group (n = 45)	t/χ^2	*P* value
Age (years)	69.3 ± 7.2	69.9 ± 7.2	68.1 ± 7.0	1.354	0.179
Height (cm)	162.62 ± 7.58	163.10 ± 7.39	161.78 ± 7.91	0.918	0.361
Weight (kg)	64.24 ± 10.56	65.62 ± 10.74	61.78 ± 9.86	2.027	0.045
BMI	24.41 ± 4.44	24.84 ± 4.76	23.64 ± 3.71	1.563	0.121
Disease_Duration_Months	31.33 ± 13.28	29.73 ± 13.06	34.18 ± 13.35	-1.804	0.075
Stroke_Onset_Months	37.04 ± 15.58	37.46 ± 16.67	36.29 ± 13.59	0.426	0.671
VP_Diagnosis_Months	31.02 ± 11.23	29.96 ± 10.66	32.91 ± 12.08	-1.366	0.176
Gender					
Male	52 (41.6%)	31 (38.8%)	21 (46.7%)	0.453	0.501
Female	73 (58.4%)	49 (61.3%)	24 (53.3%)	0.453	0.501
Education level					
Low	31 (24.8%)	18 (22.5%)	13 (28.9%)	1.262	0.532
Medium	61 (48.8%)	42 (52.5%)	19 (42.2%)	1.262	0.532
High	33 (26.4%)	20 (25.0%)	13 (28.9%)	1.262	0.532
Smoking history					
No	97 (77.6%)	66 (82.5%)	31 (68.9%)	2.336	0.126
Yes	28 (22.4%)	14 (17.5%)	14 (31.1%)	2.336	0.126
Drinking history					
No	99 (79.2%)	62 (77.5%)	37 (82.2%)	0.156	0.693
Yes	26 (20.8%)	18 (22.5%)	8 (17.8%)	0.156	0.693
Hypertension history				20.581	< 0.001
Yes	54 (43.2%)	22 (27.5%)	32 (71.1%)		
No	71 (56.8%)	58 (72.5%)	13 (28.9%)		
Diabetes mellitus history					
No	72 (57.6%)	44 (55.0%)	28 (62.2%)	0.355	0.551
Yes	53 (42.4%)	36 (45.0%)	17 (37.8%)	0.355	0.551
Hyperlipidemia history					
Yes	57 (45.6%)	34 (42.5%)	23 (51.1%)	0.549	0.459
No	68 (54.4%)	46 (57.5%)	22 (48.9%)	0.549	0.459
Coronary heart disease history					
No	99 (79.2%)	59 (73.8%)	40 (88.9%)	3.140	0.076
Yes	26 (20.8%)	21 (26.2%)	5 (11.1%)	3.140	0.076
Stroke type					
Ischemic	97 (77.6%)	62 (77.5%)	35 (77.8%)	0.208	0.901
Hemorrhagic	21 (16.8%)	13 (16.2%)	8 (17.8%)	0.208	0.901
Mixed	7 (5.6%)	5 (6.2%)	2 (4.4%)	0.208	0.901
Key stroke location					
Cortical	65 (52.0%)	37 (46.2%)	28 (62.2%)	2.957	0.228
Subcortical	31 (24.8%)	22 (27.5%)	9 (20.0%)	2.957	0.228
Brainstem	29 (23.2%)	21 (26.2%)	8 (17.8%)	2.957	0.228
Fazekas_Score					
0	22 (17.6%)	11 (13.8%)	11 (24.4%)	4.120	0.249
1	24 (19.2%)	14 (17.5%)	10 (22.2%)	4.120	0.249
2	36 (28.8%)	27 (33.8%)	9 (20.0%)	4.120	0.249
3	43 (34.4%)	28 (35.0%)	15 (33.3%)	4.120	0.249

Initial motor symptom					
Tremor	56 (44.8%)	39 (48.8%)	17 (37.8%)	2.252	0.522
Rigidity	29 (23.2%)	19 (23.8%)	10 (22.2%)	2.252	0.522
Bradykinesia	26 (20.8%)	14 (17.5%)	12 (26.7%)	2.252	0.522
Postural instability	14 (11.2%)	8 (10.0%)	6 (13.3%)	2.252	0.522
Dopamine agonist use					
Yes	57 (45.6%)	35 (43.8%)	22 (48.9%)	0.134	0.714
No	68 (54.4%)	45 (56.2%)	23 (51.1%)	0.134	0.714
Benzodiazepine use					
No	90 (72.0%)	57 (71.2%)	33 (73.3%)	0.002	0.967
Yes	35 (28.0%)	23 (28.7%)	12 (26.7%)	0.002	0.967
Baseline Hoehn & Yahr stage	2.26 ± 0.88	2.42 ± 0.91	1.97 ± 0.76	2.967	0.004
LEDD_mg	456.98 ± 161.94	483.77 ± 166.57	409.33 ± 143.06	2.629	0.010
UPDRS_Total	64.16 ± 22.77	74.99 ± 15.65	44.91 ± 20.72	8.473	< 0.001
UPDRS_I_Mentation	5.90 ± 3.41	7.39 ± 2.75	3.24 ± 2.83	7.934	< 0.001
UPDRS_II_ADL	19.30 ± 9.53	23.57 ± 7.87	11.71 ± 7.27	8.500	< 0.001
UPDRS_III_Motor	32.34 ± 13.37	35.80 ± 11.33	26.20 ± 14.59	3.814	< 0.001
UPDRS_IV_Complications	6.62 ± 3.91	8.22 ± 3.32	3.76 ± 3.19	7.407	< 0.001
PDQ39_Score	45.61 ± 17.87	43.41 ± 18.79	49.51 ± 15.53	-1.951	0.054
CSF_Alpha_Synuclein	549.30 ± 143.08	595.16 ± 138.56	467.76 ± 112.25	5.587	< 0.001
IL6	4.46 ± 1.99	5.26 ± 1.85	3.05 ± 1.35	7.675	< 0.001
TNF_alpha	6.99 ± 3.35	8.40 ± 3.02	4.49 ± 2.29	8.140	< 0.001
CRP	4.51 ± 2.81	5.61 ± 2.58	2.57 ± 2.06	7.217	< 0.001

Abbreviations: VP, vascular parkinsonism; BMI, body mass index; LEDD, levodopa equivalent daily dose; UPDRS, Unified Parkinson's Disease Rating Scale; UPDRS-I, UPDRS Part I (mentation, behavior, and mood); UPDRS-II, UPDRS Part II (activities of daily living); UPDRS-III, UPDRS Part III (motor function examination); UPDRS-IV, UPDRS Part IV (treatment complications); PDQ-39, Parkinson's Disease Questionnaire-39; CSF α-synuclein, cerebrospinal fluid alpha-synuclein; IL-6, interleukin-6; TNF-α, tumor necrosis factor-alpha; CRP, C-reactive protein; HAMA, Hamilton Anxiety Rating Scale; HAMD, Hamilton Depression Rating Scale.

in the complete model (**Figure 4B**), the above associations attenuated (insomnia: OR = 2.742, 95% CI 0.986-7.628, P = 0.053; RBD: OR = 2.195, 95% CI 0.659-7.313, P = 0.201), while age remained statistically significant (OR = 1.073, 95% CI 1.003-1.148, P = 0.042). Notably, the OR for the LEDD in the complete model was 1.000 (95% CI 0.997-1.003, P = 0.982), which contrasts with its association with RBD in univariate analysis (OR = 1.004, 95% CI 1.001-1.006, P = 0.019; **Table 2**), suggesting that its independent prognostic effect is primarily mediated by white matter lesions, neuroinflammation, and α-synuclein pathology. None of the biomarkers reached statistical significance in the complete model.

Quality of life outcomes assessed via PDQ-39 are shown in Table S3. The subgroup with RBD and insomnia had the lowest PDQ-39 score (37.73 ± 14.99) and the highest incidence of poor prognosis (68.2%); while the subgroup without sleep disorder had the highest PDQ-39 score (49.51 ± 15.53) and the lowest poor-prognosis rate (11.1%).

Association with white matter lesions and biomarkers

The severity of RBD was weakly but significantly positively correlated with white matter lesion burden (Fazekas score, r = 0.180, P = 0.045; **Figure 5**). The overall difference in Fazekas scores among the sleep disorder subgroups was borderline significant (ANOVA F = 2.592, P = 0.056), with the RBD and insomnia group having the highest mean score (2.36 ± 0.85; **Figure 6**).

Significant differences in biomarker levels were observed among the subgroups (**Figure 7**). Compared with the group without sleep disorders (467.76 ± 112.25 pg/mL) and the group with simple insomnia (486.91 ± 99.30 pg/mL),

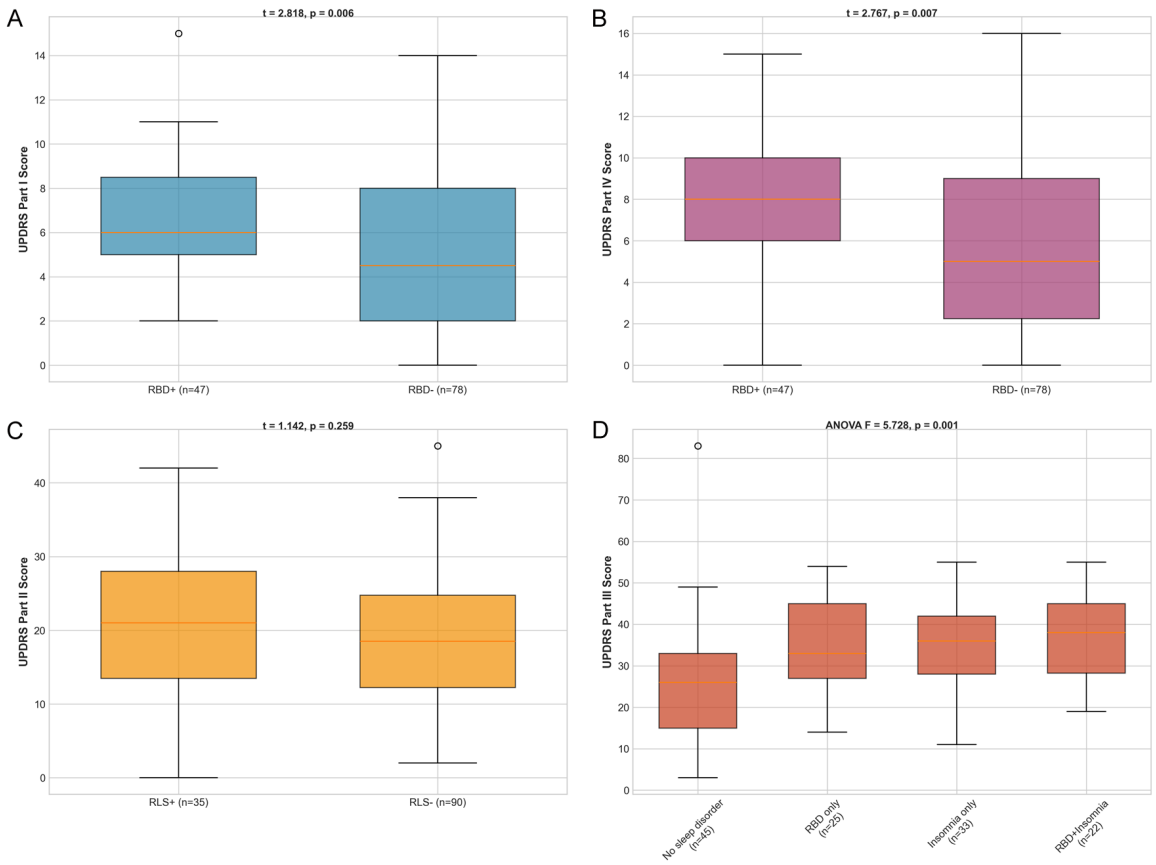

Figure 3. Associations between sleep disorders and clinical symptoms. A. Comparison of UPDRS Part I scores between RBD-positive and RBD-negative patients. B. Comparison of UPDRS Part IV scores between RBD-positive and RBD-negative patients. C. Comparison of UPDRS Part II scores between RLS-positive and RLS-negative patients. D. Comparison of UPDRS Part III scores among different sleep disorder subgroups. Abbreviations: RBD, REM sleep behavior disorder; RLS, restless legs syndrome; UPDRS, Unified Parkinson's Disease Rating Scale; UPDRS-I, UPDRS Part I (mentation, behavior, and mood); UPDRS-II, UPDRS Part II (activities of daily living); UPDRS-III, UPDRS Part III (motor function examination); UPDRS-IV, UPDRS Part IV (treatment complications).

Table 2. Factors independently associated with sleep disorders (significant factors)

Sleep Disorder	Factor	Category	OR (95% CI) or *p*-value	*P* Value
Insomnia	HAMA	Continuous	1.175 (1.102-1.253)	< 0.001
Insomnia	HAMD	Continuous	1.189 (1.107-1.277)	< 0.001
Insomnia	IL6	Continuous	1.848 (1.434-2.382)	< 0.001
Insomnia	TNF_alpha	Continuous	1.456 (1.256-1.687)	< 0.001
Insomnia	CRP	Continuous	1.394 (1.194-1.627)	< 0.001
RBD	LEDD_mg	Continuous	1.004 (1.001-1.006)	0.019
RBD	HAMA	Continuous	1.126 (1.063-1.193)	< 0.001
RBD	HAMD	Continuous	1.136 (1.064-1.212)	0.001
RBD	CSF_Alpha_Synuclein	Continuous	1.017 (1.011-1.022)	< 0.001
RBD	IL6	Continuous	1.453 (1.175-1.797)	0.004
RBD	TNF_alpha	Continuous	1.244 (1.101-1.406)	0.004
RBD	CRP	Continuous	1.294 (1.120-1.494)	0.004

Abbreviations: RBD, REM sleep behavior disorder; RLS, restless legs syndrome; OSAS, obstructive sleep apnea syndrome; PLM, periodic limb movement disorder; UPDRS-III, UPDRS Part III (motor examination); HAMA, Hamilton Anxiety Rating Scale; HAMD, Hamilton Depression Rating Scale; IL-6, interleukin-6; TNF-α, tumor necrosis factor-alpha; CRP, C-reactive protein; BMI, body mass index; LEDD, levodopa equivalent daily dose; CSF α-synuclein, cerebrospinal fluid alpha-synuclein; OR, odds ratio; CI, confidence interval.

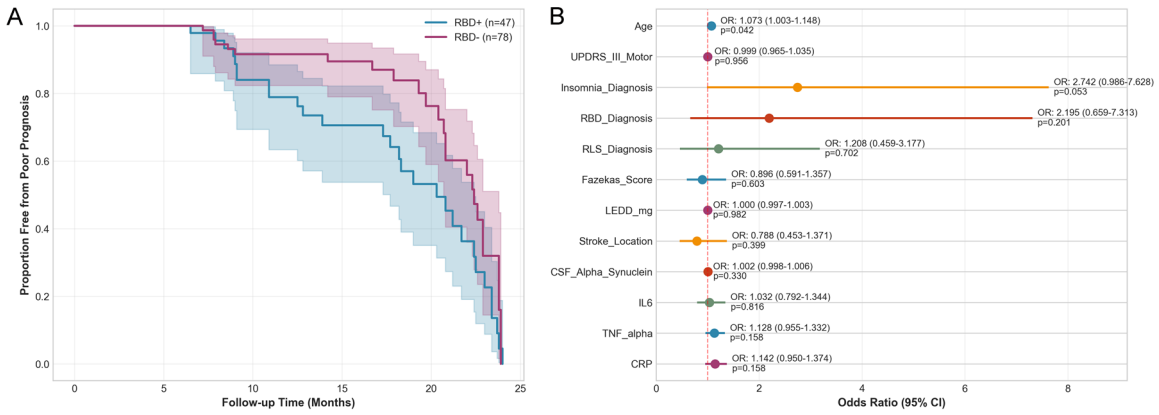

Figure 4. Impact of sleep disorders on prognosis. A. Kaplan-Meier curves comparing cumulative incidence of poor prognosis between RBD-positive and RBD-negative patients. B. Forest plot of multivariate logistic regression (full model including biomarkers and imaging) for factors associated with poor prognosis. Abbreviations: RBD, REM sleep behavior disorder; UPDRS-III, Unified Parkinson's Disease Rating Scale Part III (motor examination); RLS, restless legs syndrome; Fazekas, Fazekas scale (white matter lesion severity); LEDD, levodopa equivalent daily dose; CSF α-synuclein, cerebrospinal fluid alpha-synuclein; IL-6, interleukin-6; TNF-α, tumor necrosis factor-alpha; CRP, C-reactive protein; CI, confidence interval.

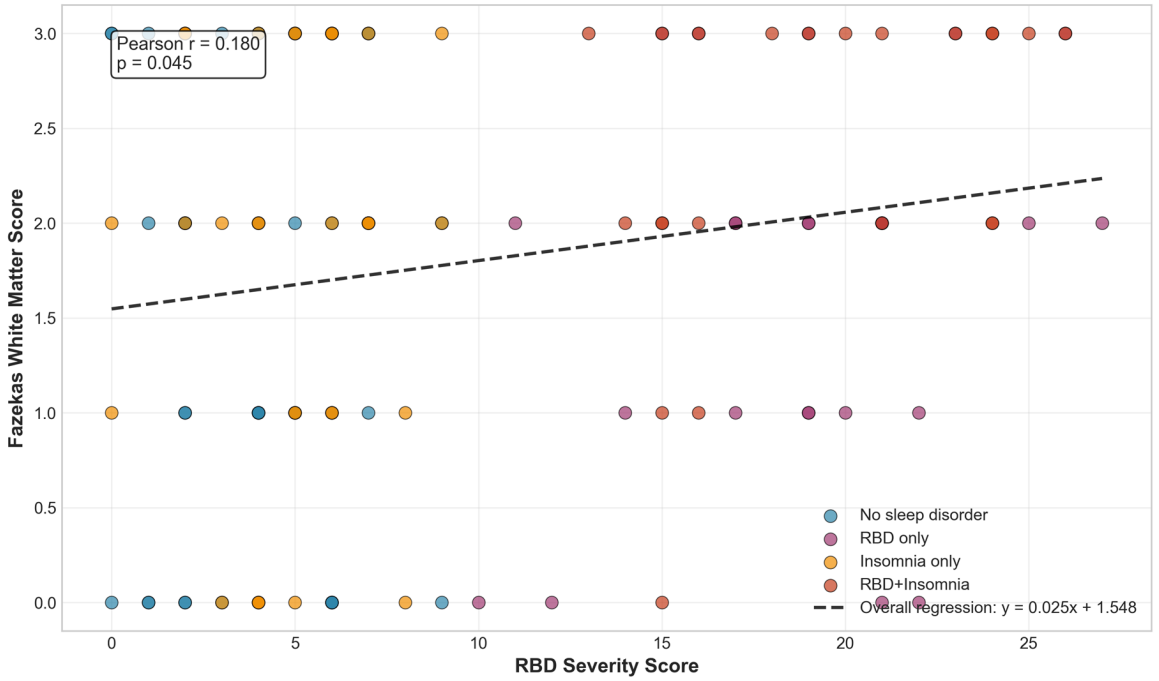

Figure 5. Correlation between RBD severity and white matter lesion burden. Abbreviations: RBD, REM sleep behavior disorder; Fazekas, Fazekas scale; UPDRS-III, Unified Parkinson's Disease Rating Scale Part III (motor examination).

the subgroup with combined RBD (RBD alone: 661.20 ± 93.59 pg/mL, RBD combined with insomnia: 682.50 ± 124.84 pg/mL) had significantly higher CSF α-synuclein concentrations (ANOVA F = 32.412, P < 0.001; **Figure 7A**). Similarly, the inflammatory markers IL-6 (**Figure 7B**), TNF-α (**Figure 7C**), and CRP (**Figure 7D**) were all significantly elevated in the subgroup associated with RBD (all P < 0.001). Correlation analysis showed that CSF α-synuclein was not significantly correlated with Fazekas scores (r = 0.054, P = 0.550; **Figure 8A**), whereas IL-6 (r = 0.172, P = 0.055; **Figure 8B**), TNF-α (r = 0.240, P = 0.007; **Figure 8C**), and CRP (r = 0.201, P =

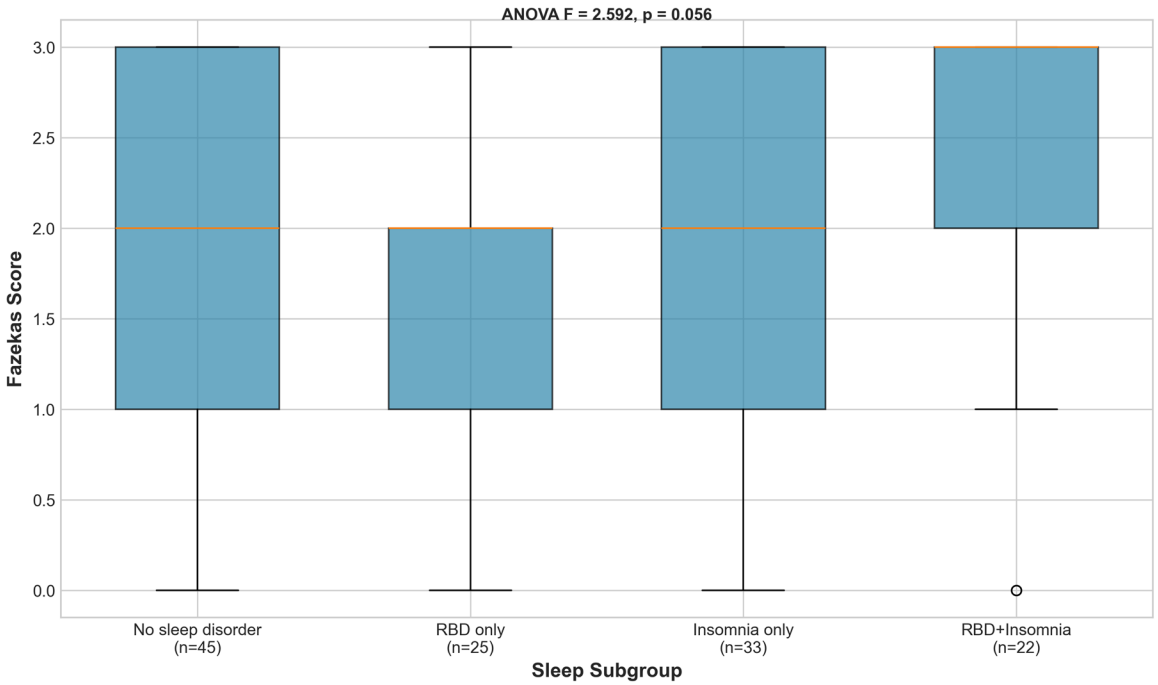

Figure 6. Fazekas score by sleep disorder subgroup. Abbreviations: Fazekas, Fazekas scale; RBD, REM sleep behavior disorder.

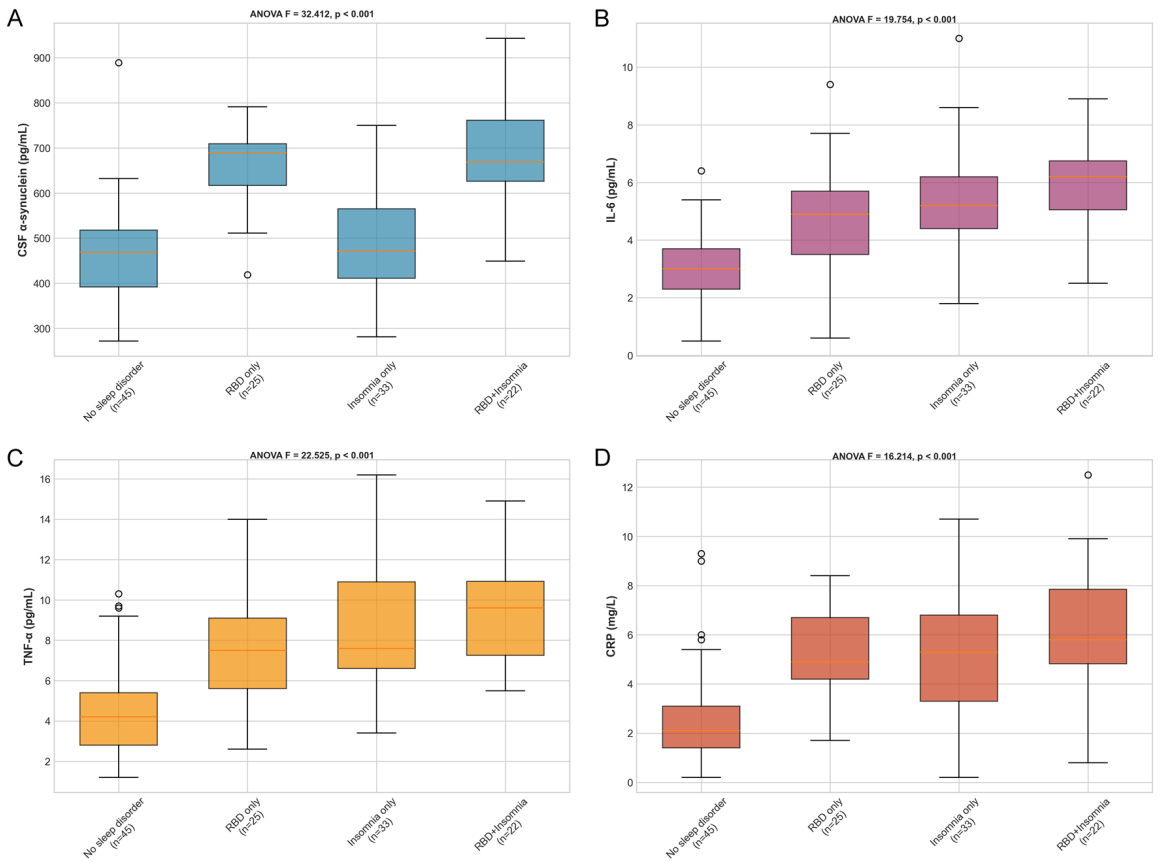

Figure 7. Biomarker levels by sleep disorder subgroup. A. CSF α-synuclein levels across sleep disorder subgroups. B. IL-6 levels across sleep disorder subgroups. C. TNF-α levels across sleep disorder subgroups. D. CRP levels across sleep disorder subgroups. Abbreviations: CSF α-synuclein, cerebrospinal fluid alpha-synuclein; IL-6, interleukin-6; TNF-α, tumor necrosis factor-alpha; CRP, C-reactive protein; RBD, REM sleep behavior disorder.

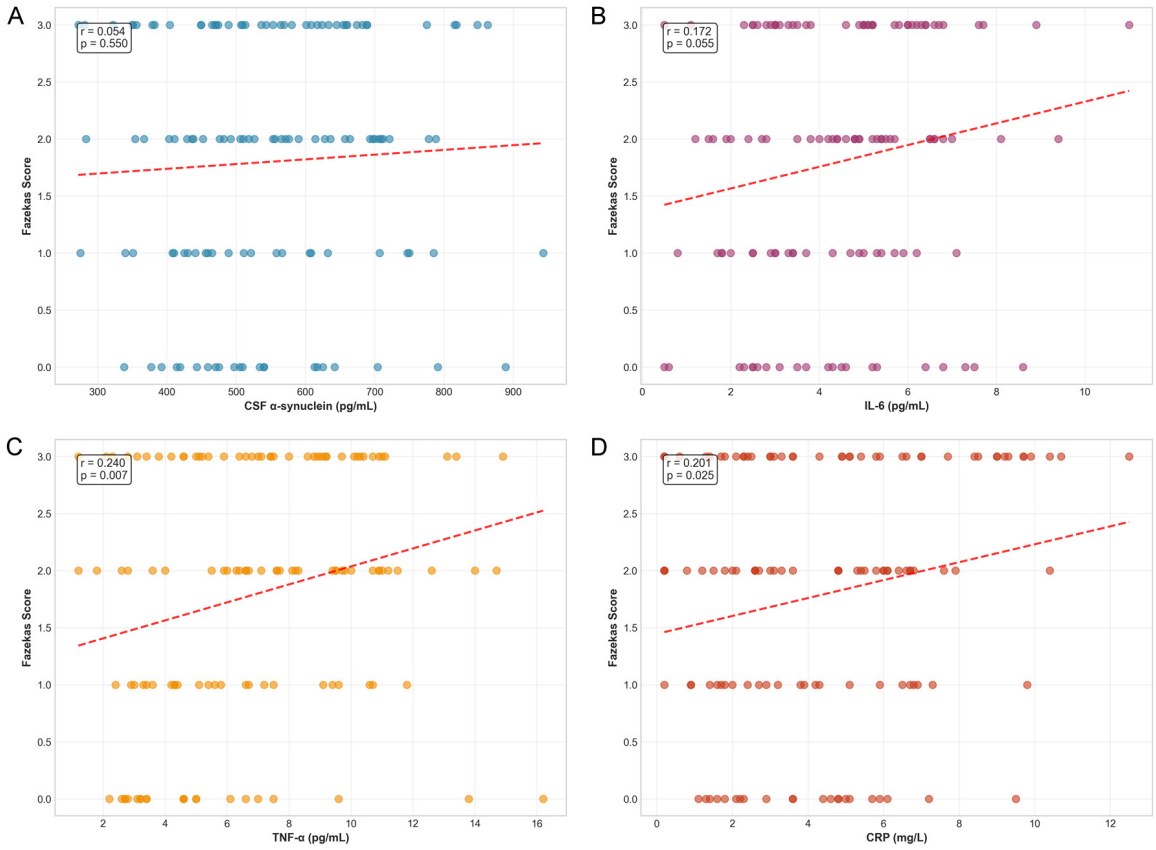

Figure 8. Correlations between biomarkers and white matter lesion burden. A. Correlation between CSF α-synuclein and Fazekas score. B. Correlation between IL-6 and Fazekas score. C. Correlation between TNF-α and Fazekas score. D. Correlation between CRP and Fazekas score. Abbreviations: CSF α-synuclein, cerebrospinal fluid alpha-synuclein; IL-6, interleukin-6; TNF-α, tumor necrosis factor-alpha; CRP, C-reactive protein; Fazekas, Fazekas scale.

0.025; **Figure 8D**) were positively correlated with Fazekas scores. Detailed subgroup comparisons including data from each item and biomarker of the UPDRS are shown in **Table 3**. In addition, correlation analysis indicated that IL-6, TNF-α, and CRP were all significantly positively correlated with the severity of RBD and the ISI (all $P < 0.001$; Table S4).

Discussion

This study focuses on the specific population of VP to systematically elucidate the clinical spectrum of sleep disorders in this syndrome and their prognostic significance. Although sleep disorders are widely recognized as a core non-motor symptom of idiopathic PD, and RBD has become an important prognostic marker of α-synucleinosis, the manifestations, pathophysiological mechanisms, and prognostic significance of sleep disorders in VP patients remain poorly understood [19-22]. Unlike PD, VP is mainly caused by cerebrovascular lesions and has unique clinical phenotypes and treatment response characteristics. Recent limited studies have shown a high incidence of sleep disorders in VP patients, but key questions remain unanswered: What is the specific distribution of sleep disorder subtypes [23]? How are these disorders associated with cerebrovascular lesion characteristics (such as lesion location and white matter burden) [24-27]? How are they related to motor/non-motor symptoms and clinical outcomes [28, 29]? Of

Table 3. Comparison of clinical, imaging, and biomarker characteristics among VP patients with different sleep disorder subtypes

Variable	Insomnia only (n = 33)	RBD only (n = 25)	Insomnia+RBD (n = 22)	No sleep disorder (n = 45)	F/χ^2	*P* Value
Age	70.4 ± 7.5	70.7 ± 5.8	68.3 ± 8.2	68.1 ± 7.0	1.105	0.350
Disease_Duration_Months	28.03 ± 13.84	30.96 ± 13.46	30.86 ± 11.59	34.18 ± 13.35	1.397	0.247
UPDRS_Total	77.06 ± 17.73	73.12 ± 15.01	74.00 ± 13.14	44.91 ± 20.72	27.931	< 0.001
UPDRS_I_Mentation	8.09 ± 2.82	6.64 ± 2.81	7.18 ± 2.42	3.24 ± 2.83	23.040	< 0.001
UPDRS_II_ADL	25.24 ± 8.87	24.00 ± 7.58	20.59 ± 5.79	11.71 ± 7.27	25.320	< 0.001
UPDRS_III_Motor	34.88 ± 11.38	35.44 ± 11.33	37.59 ± 11.59	26.20 ± 14.59	5.728	0.001
UPDRS_IV_Complications	8.85 ± 3.06	7.04 ± 3.36	8.64 ± 3.43	3.76 ± 3.19	19.965	< 0.001
LEDD_mg	439.27 ± 162.37	515.68 ± 190.58	514.27 ± 131.87	409.33 ± 143.06	3.665	0.014
HAMA	15.45 ± 6.02	14.12 ± 7.10	19.41 ± 4.84	7.20 ± 5.76	24.703	< 0.001
HAMD	14.67 ± 5.63	13.44 ± 4.91	18.36 ± 4.76	8.00 ± 5.83	20.842	< 0.001
PDQ39_Score	44.55 ± 20.35	46.92 ± 19.21	37.73 ± 14.99	49.51 ± 15.53	2.296	0.081
Fazekas_Score	1.79 ± 1.11	1.64 ± 0.99	2.36 ± 0.85	1.62 ± 1.19	2.592	0.056
CSF_Alpha_Synuclein	486.91 ± 99.30	661.20 ± 93.59	682.50 ± 124.84	467.76 ± 112.25	32.412	< 0.001
IL6	5.21 ± 1.89	4.68 ± 1.93	6.00 ± 1.49	3.05 ± 1.35	19.754	< 0.001
TNF_alpha	8.38 ± 3.10	7.37 ± 2.82	9.60 ± 2.78	4.49 ± 2.29	22.525	< 0.001
CRP	5.48 ± 2.86	5.20 ± 1.83	6.26 ± 2.84	2.57 ± 2.06	16.214	< 0.001

Abbreviations: VP, vascular parkinsonism; UPDRS, Unified Parkinson's Disease Rating Scale; UPDRS-I, UPDRS Part I (mentation, behavior, and mood); UPDRS-II, UPDRS Part II (activities of daily living); UPDRS-III, UPDRS Part III (motor function examination); UPDRS-IV, UPDRS Part IV (treatment complications); LEDD, levodopa equivalent daily dose; HAMA, Hamilton Anxiety Rating Scale; HAMD, Hamilton Depression Rating Scale; PDQ-39, Parkinson's Disease Questionnaire-39; Fazekas, Fazekas scale; CSF α-synuclein, cerebrospinal fluid alpha-synuclein; IL-6, interleukin-6; TNF-α, tumor necrosis factor-alpha; CRP, C-reactive protein.

particular concern is whether the presence of multiple cerebrovascular risk factors and diffuse white matter lesions in VP patients leads to a unique sleep disorder pattern? Are these disorders related to specific brain network damage? Do different types of sleep disorders (such as RBD, insomnia, and OSAS) have different predictive value for VP progression? Solving these questions has become a critical task in this field [30, 31].

This study systematically depicts the comprehensive sleep disorder spectrum in VP patients for the first time, including insomnia, RBD, RLS, and OSAS, and explores their association with clinical symptoms, neuroimaging markers, and prognosis. The main findings are as follows: (1) The prevalence of sleep disorders in VP patients was extremely high (64.0%), with insomnia (44.0%) and RBD (37.6%) being the most common subtypes. (2) RBD was independently associated with more severe neuropsychiatric and behavioral symptoms (UPDRS) and more treatment-related complications (UPDRS Part IV), whereas insomnia was closely associated with increased anxiety and depression burden. (3) In the core multivariate model adjusting only for clinical variables, both RBD and insomnia were strong independent predictors of poor prognosis within one year. However, after further adjustment for biomarkers and imaging markers (white matter lesion severity, levodopa equivalent daily dose, stroke location, and levels of CSF α-synuclein, IL-6, TNF-α, and CRP), the associations weakened and were no longer statistically significant, while age remained an independent predictor. (4) Notably, CSF α-synuclein and inflammatory cytokines (IL-6, TNF-α, CRP) were markedly elevated in the subgroup of patients with RBD. IL-6 showed a borderline positive correlation with white matter lesion burden (Fazekas score), while TNF-α and CRP showed significant positive correlations. Furthermore, the levels of IL-6, TNF-α, and CRP were all positively correlated with the severity of RBD and the Insomnia Severity Index (ISI), suggesting a dose-dependent relationship between inflammation level and the severity of sleep disorders. These findings provide new evidence for a pathophysiological link between sleep disorders, neuroinflammation, α-synuclein pathology, and cerebrovascular injury in VP patients.

The high incidence of RBD in this study warrants further investigation. In the field of neuro-

degenerative diseases, RBD is considered a highly specific precursor marker of alpha-synucleinosis. However, in this group of VP patients, the incidence of RBD was still significantly higher than in the general elderly population. This suggests that, in addition to classic synucleinosis, cerebrovascular lesions themselves may also induce similar RBD manifestations. Potential mechanisms include direct ischemic damage to brainstem sleep regulation nuclei (such as the subcoeruleus nucleus and dorsal pontine tegmentum), or damage to white matter fiber tracts connecting the brainstem to the basal ganglia and limbic system, leading to weakened normal inhibition of muscle tone during rapid eye movement sleep. This study found a positive correlation between the severity of RBD and white matter lesion burden, providing partial evidence for the latter mechanism. This suggests that RBD may serve as a "common pathway" of dysfunction in multiple brain regions, rather than being associated with only a specific neurodegenerative disease. It is noteworthy that CSF α-synuclein levels were not correlated with white matter lesions, indicating that in VP, the effect of white matter lesions on sleep may be mainly achieved through neuroinflammatory pathways rather than α-synuclein deposition. As Jellinger et al. [32] described in their review, VP is characterized by extensive deep white matter lesions caused by small vessel lesions, which may disrupt neural circuits involved in sleep regulation. The strong correlation between insomnia and poor prognosis observed in the core model of VP may reflect a vicious cycle within the comorbidity network of mood and sleep disorders. In the present study, patients with insomnia had significantly higher (HAMA and HAMD scores). Chronic insomnia can lead to hypothalamic-pituitary-adrenal axis dysfunction, elevated levels of pro-inflammatory cytokines, and impaired prefrontal cortex function. These changes not only exacerbate mood disorders, but may also accelerate the overall progression of VP by impairing neuroplasticity and deteriorating vascular endothelial function. Therefore, clinicians should regard insomnia in VP patients as a warning sign of potential mood disorders and adopt comprehensive management strategies. Recent research evidence suggests that RBD may be associated with glymphatic system dysfunction, leading to impaired clearance of α-synuclein and other metabolites [33], which aligns with the results of elevated CSF α-synuclein levels in the RBD subgroup in this study.

This study did not find RLS to be an independent predictor of poor prognosis in VP. This result differs from some studies reported on idiopathic Parkinson's disease (PD), which may reflect a fundamental difference in the pathological mechanisms between VP and PD. In VP, RLS may primarily manifest as a relatively independent complication, associated with iron metabolism abnormalities and dopaminergic dysfunction, with limited impact on the core disease progression trajectory.

A particularly important finding of this study is that the predictive power of insomnia and RBD was weakened after incorporating biomarkers and imaging indicators. In the complete multivariate model, insomnia and RBD were no longer statistically significant, and age became the only independent predictor, with all biomarkers failing to reach statistical significance. These results suggest that the impact of sleep disorders on prognosis may be at least partially mediated through neuroinflammatory responses, α-synuclein pathological changes, and white matter damage. The subgroup of patients with RBD had markedly elevated CSF α-synuclein levels and higher levels of IL-6, TNF-α, and CRP; moreover, IL-6, TNF-α, and CRP were positively correlated with Fazekas scores. These results support a pathological model: sleep disorders (especially RBD) are associated with increased α-synuclein load and neuroinflammation, thereby promoting white matter lesions and accelerating disease progression. Although the biomarkers themselves did not retain independent predictive significance in the holistic regression model (which may be related to the limited sample size and collinearity among the indicators), their strong correlation in univariate analysis provides strong evidence for the mediating effect. Future studies with large samples and longitudinal designs are needed to formally validate this mediating effect and clarify whether targeting these molecular pathways can improve the prognosis of VP patients. Furthermore, after adjusting for multiple confounding factors, CRP remained independently associated with insomnia and RBD, with a stronger effect on insomnia, suggesting that in VP patients, the effect of systemic inflamma-

tion on insomnia may be more significant than on RBD.

This study has clear clinical translational value. First, we demonstrated that simple tools such as the ISI and the RBD Questionnaire can be used to rapidly and economically screen VP patients and related sleep disorders in routine outpatient settings. Those with positive screening results, especially those with RBD or severe insomnia, should be considered high-risk for rapid disease progression. We recommend the following stratified management strategy: increasing the frequency of clinical follow-up and closely monitoring changes in neurological function; performing PSG when conditions permit to confirm the diagnosis, especially for suspected RBD or OSAS; and initiating individualized interventions as early as possible. For example, continuous positive airway pressure therapy in patients diagnosed with OSAS can improve daytime sleepiness and cognitive function and may also reduce the risk of vascular events. For insomnia patients with anxiety and depression, cognitive behavioral therapy for insomnia or medication after careful evaluation can be used. Currently, there is an urgent need to conduct prospective intervention studies to verify whether this sleep management-centered strategy can effectively delay the progression of VP.

This study does have several limitations. First, this is a single-center retrospective study, inevitably subject to selection bias. Second, the diagnosis of sleep disorders mainly relies on scale assessments, supplemented by some PSG data, but not all patients have been verified by the "gold standard" PSG examination, which may affect the accuracy of sleep disorder subtype classification. Third, the sample size is limited; the sample size of some subgroups (such as patients with specific sleep disorder combinations) is insufficient, which may affect the statistical power and prevent formal mediation effect analysis. Fourth, the confounding effects of drug treatments (such as dopaminergic drugs and benzodiazepines) on the clinical manifestations and assessment results of sleep disorders have not been completely ruled out. Finally, although this study detected several candidate biomarkers, it did not evaluate other potentially related molecules (such as phosphorylated tau protein and neurofilament light chains). Including such indicators may provide more evidence for mechanistic studies.

Conclusion

In conclusion, this study confirms that VP patients have a higher incidence of sleep disorders and identifies RBD and insomnia as independent predictors of poor prognosis, both of which can increase the risk of adverse outcomes substantially. These findings support the inclusion of routine sleep assessment in the clinical management of VP. Early identification and targeted intervention of these sleep disorders may help delay disease progression and improve patient prognosis. Further prospective studies are needed to validate the conclusions of this study and explore the therapeutic value of sleep-centered interventions in VP.

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Disclosure of conflict of interest

None.

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Table S1. Multivariate logistic regression analysis of C-reactive protein (CRP) for insomnia and REM sleep behavior disorder (RBD)

Outcome	OR (95% CI)	*P* Value	Number of observations	Number of events
Insomnia	1.354 (1.153-1.589)	< 0.001	125	55
RBD	1.238 (1.063-1.442)	0.006	125	47

Abbreviations: OR, odds ratio; CI, confidence interval; RBD, REM sleep behavior disorder.

Table S2. Multivariate logistic regression analysis (core model) for factors associated with poor prognosis

Variable	OR (95% CI)	*P* Value
Age	1.071 (1.007-1.140)	0.028
UPDRS-III motor score	1.007 (0.974-1.041)	0.673
Insomnia	4.489 (1.903-10.589)	< 0.001
RBD	4.318 (1.814-10.280)	< 0.001
RLS	1.243 (0.498-3.105)	0.641

Abbreviations: UPDRS-III, UPDRS Part III (motor examination); RBD, REM sleep behavior disorder; RLS, restless legs syndrome; OR, odds ratio; CI, confidence interval.

Table S3. PDQ-39 scores and poor prognosis rates by sleep disorder subgroup

Subgroup	N	PDQ39_Score (Mean ± SD)	Test_Statistic (t)	*P*-value vs No sleep disorder	Poor Prognosis (%)
No sleep disorder	45	49.51 ± 15.53	Reference	Reference	11.1% (5/45)
Insomnia only	33	44.55 ± 20.35	-1.173	0.737	54.5% (18/33)
RBD only	25	46.92 ± 19.21	-0.578	1.000	56.0% (14/25)
RBD+Insomnia	22	37.73 ± 14.99	-2.986	0.014	68.2% (15/22)

Abbreviations: PDQ-39, Parkinson's Disease Questionnaire-39; RBD, REM sleep behavior disorder.

Table S4. Pearson correlation coefficients between inflammatory markers and sleep disorder severity

Biomarker	Sleep Disorder Severity	Pearson r	*P* Value
IL6	RBD Severity	0.328	< 0.001
IL6	Insomnia Severity (ISI)	0.446	< 0.001
TNF_alpha	RBD Severity	0.301	< 0.001
TNF_alpha	Insomnia Severity (ISI)	0.513	< 0.001
CRP	RBD Severity	0.310	< 0.001
CRP	Insomnia Severity (ISI)	0.399	< 0.001

Abbreviations: IL-6, interleukin-6; TNF-α, tumor necrosis factor-alpha; CRP, C-reactive protein; RBD, REM sleep behavior disorder; ISI, Insomnia Severity Index.