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Classifying Parkinson's Disease With or Without Rapid Eye Movement Sleep Behavior Disorder Using Machine Learning-Based Analysis of Single-Lead Electrocardiogram

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Background and Objective Rapid eye movement sleep behavior disorder is a prodromal stage of alpha-synucleinopathy. Parkinson's disease with rapid eye movement sleep behavior disorder is associated with more severe symptoms and cerebral pathology compared to Parkinson's disease without rapid eye movement sleep behavior disorder. This study classified idiopathic rapid eye movement sleep behavior disorder, Parkinson's disease with rapid eye movement sleep behavior disorder, and Parkinson's disease without rapid eye movement sleep behavior disorder using single-lead electrocardiogram signals from polysomnography.

Methods Subjects who underwent polysomnography and dopamine transporter positron emission tomography between January 2010 and December 2021 were retrospectively analyzed. The study included 4 patients with idiopathic rapid eye movement sleep behavior disorder, 9 with Parkinson's disease with rapid eye movement sleep behavior disorder, 8 with Parkinson's disease without rapid eye movement sleep behavior disorder, 9 control subjects, and 15 healthy controls. Heart rate variability features were extracted from electrocardiogram signals, and machine learning models classified the groups.

Results No significant differences in demographics or obstructive sleep apnea severity were found between the groups, except for healthy controls. Machine learning classifiers effectively distinguished idiopathic rapid eye movement sleep behavior disorder, Parkinson's disease with rapid eye movement sleep behavior disorder, and Parkinson's disease without rapid eye movement sleep behavior disorder based on electrocardiogram features.

Conclusions This study demonstrated the potential of single-lead electrocardiogram signals to differentiate idiopathic rapid eye movement sleep behavior disorder, Parkinson's disease with rapid eye movement sleep behavior disorder, and insight for future prospective studies to predict the conversion.

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Keywords Polysomnography; Sleep, REM; REM sleep behavior disorder; Parkinson disease; Conversion.

INTRODUCTION

Rapid eye movement (REM) sleep behavior disorder (RBD) has been suggested as a strong predictor of alpha-synucleinopathies, such as Parkinson's disease (PD), dementia with Lewy bodies (DLB), and multiple system atrophy (MSA). The conversion rate from RBD to an alpha-synucleinopathy has been reported as 6.3% per year, resulting in a 73.5% conversion after 12 years [1]. The risk is notably high, with a hazard ratio (HR) of 1.54 for REM sleep without atonia (RWA), which is comparable to the HR of 1.98 for an abnormal dopamine transporter scan.

Within PD patients, there are those who have had previous or concurrent RBD (PDRBD) and those who have never experienced RBD (PDnoRBD). The difference between these subtypes is thought to stem from pathological differences in the two types of PD: the brain-first type and the body-first type. RBD, with its pathophysiological basis in the degeneration of the subcoeruleus nucleus and associated circuits in the medulla and pons, is presumed to be more strongly associated with the body-first type of PD, in line with its ascending neurodegeneration pathway [2]. This distinction is crucial, as the body-first type of PD is associated with more malignant symptoms and more severe cerebral pathology [3].

The diagnosis of RBD according to the International Classification of Sleep Disorders, Third Edition (ICSD-3) requires documented repeated episodes of sleep-related vocalization and/or complex motor behaviors, as well as polysomnography (PSG) evidence of RWA [4]. While PSG is the gold standard for RBD diagnosis, the process is labor-intensive and accessibility is limited in certain areas. These challenges are further compounded for individuals with gait disturbances or bradykinesia, such as PD patients.

There have been attempts to classify diseases based on PSG data utilizing artificial intelligence (AI). Similarly, efforts have been made to classify diseases using electrocardiogram (ECG) features from PSG recordings with considerable accuracy [5-9]. However, applying these models remains challenging due to the heterogeneity of sleep laboratories and PSG software. Given that ECG is always included in PSG and routine ECG can be performed more easily, using ECG data from PSG for disease classification is a promising approach, especially considering the predictive capabilities of AI. Moreover, alpha-synucleinopathies, such as PD, are associated with dysautonomia, which is considered to originate more peripherally than centrally [10].

Autonomic dysfunction has been observed in 83% of patients with idiopathic RBD (iRBD), intermediate between that of healthy controls (HCs) and PD patients [11]. Presence of RBD is a stronger predictor of cardiac autonomic dysfunction than PD itself [12]. More severe baseline cardiovagal autonomic dysfunction in iRBD has been associated with phenoconversion to DLB but not PD [13].

Previous studies have reported the potential to discriminate between RBD and controls using ECG, showing that heart rate variability (HRV) in iRBD is significantly decreased during wakefulness compared to controls [14]. HRV in iRBD has been associated with quantified tonic RWA, which is a possible predictor of phenoconversion [15]. However, in another study none of the HRV components was able to predict the presence of iRBD [16].

This preliminary study aims to classify iRBD, PDRBD, and PDnoRBD from those without RBD or parkinsonism, using HRV features extracted from single-lead ECG data obtained during PSG.

METHODS

Selection of Data and Labeling of RBD and PD

This study was a retrospective analysis. Internal electronic health data were queried to identify participants who had undergone both PSG and dopamine transporter positron emission tomography (PET) between January 1, 2010 and December 31, 2021. Polysomnographic findings and medical records were reviewed, and participants were excluded if they met any of the following criteria: missing raw PSG data, PSG without REM sleep, insufficient PSG with a total sleep time of less than 1 hour, known atrial fibrillation (AF) or pacemaker insertion, pseudo-RBD, duplicate studies (including titration studies), or PET results indicating an alternative diagnosis other than normal, PD, or parkinsonism, such as atypical findings or basal ganglia infarction (Fig. 1).

Participants were classified into four groups based on PET results and PSG-documented RBD diagnosis. Positive PET results were defined as those indicating parkinsonism, while negative results indicated normal findings. A positive RBD diagnosis required PSG-documented RBD according to the American Academy of Sleep Medicine (AASM) criteria at the time of interpretation. A negative RBD diagnosis was assigned to participants who did not meet the criteria for RBD and lacked RWA, regardless of the presence of dream-enactment behaviors (DEB).

Further exclusions based on PET results and medical records included cases of DLB, MSA, PD dementia, and discordant diagnoses, such as scans without evidence of dopaminergic deficit (SWEDD) or idiopathic PD (IPD) diagnosed despite normal dopamine transporter PET results. In summary, PET results were cross-referenced with electronic medical records to define IPD.

To ensure consistency, a manual matching process based on age, sex, and obstructive sleep apnea (OSA) severity was performed to select participants for the four study groups. Participants were categorized as Fig. 1. Matched control (MC) was defined as individuals who were not diagnosed with RBD and had normal dopamine transporter PET results, despite having undergone testing due to symptoms such as DEB or tremor.

Additionally, the HC group was selected from individuals who underwent PSG between January 1, 2020 and December 31, 2021. HCs were defined by an Apnea-Hypopnea Index (AHI) of less than 5 and the absence of comorbidities including hypertension, diabetes, arrhythmia, cardiovascular disease, depression, insomnia, or a history of parkinsonism, as documented in medical records.

PSG

In-laboratory overnight sleep recordings were conducted using Twin PSG Software (GRASS Technologies) from 2010 to 2017, and Natus Sleepworks (Xltek, Natus Incorporated) from 2017 to 2020. The recordings included electroencephalography (EEG) from frontal, central, and occipital electrodes, electromyography

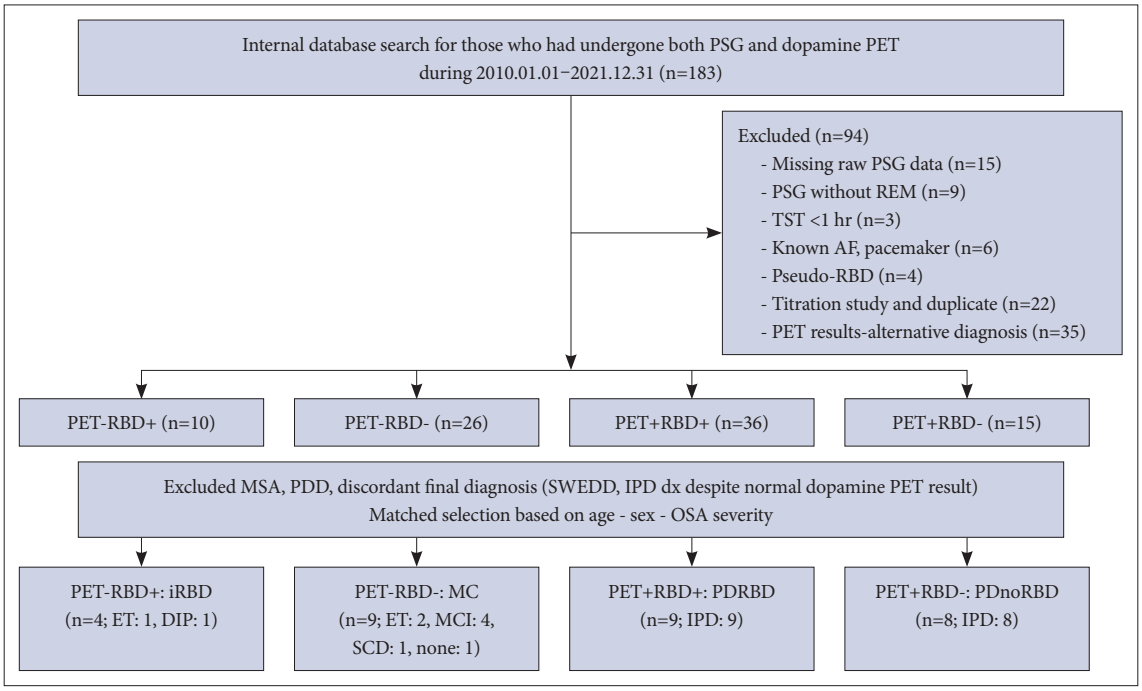

Fig. 1. Participants' selection flow diagram. PET-negative and RBD-positive: iRBD. PET-negative and RBD-negative: MC. PET-positive and RBD-positive: PDRBD. PET-positive and RBD-negative: PDnoRBD. PSG, polysomnography; PET, positron emission tomography; REM, rapid eye movement; TST, total sleep time; AF, atrial fibrillation; RBD, REM sleep behavior disorder; MSA, multiple system atrophy; PDD, Parkinson's disease dementia; SWEDD, scans without evidence of dopaminergic deficit; IPD, idiopathic Parkinson's disease; OSA, obstructive sleep apnea; iRBD, idiopathic RBD; PDRBD, Parkinson's disease with REM sleep behavior disorder; PDnoRBD, Parkinson's disease without REM sleep behavior disorder; MC, matched control; ET, essential tremor; DIP, drug Induced parkinsonism; MCI, minor cognitive impairment; SCD, subjective cognitive decline.

(EMG) from extraocular, chin, and bilateral anterior tibialis muscles, one-lead ECG, nasal airflow and thermistor, oximetry, body position, chest and abdominal plethysmography, microphones, and video monitoring. The sampling rate and the low- and high-frequency filters were configured according to the AASM guidelines. Scoring of PSG including RWA, and interpretation were performed by trained sleep technicians and specialists according to the AASM criteria relevant to the time of the PSG. RBD was defined as repeated DEB documented alongside PSG-confirmed RWA. Following the AASM update in June 2020, the revised 2.6 criteria were applied [17].

Dopamine Transporter PET

The participants underwent N-(3-[^{18}F]fluoropropyl)-2β-carbon ethoxy-3β-(4-iodophenyl) nortropane (^{18}F-FP-CIT) PET between 2010 and 2020. ^{18}F-FP-CIT PET was acquired using a Discovery 600 system (General Electric Healthcare).

Processing of ECG Data of PSG and Analysis of HRV

The PSG data was converted into European Data Format files and ECG signals were extracted for preprocessing. Preprocessing steps included signal reversal, removal of front and end signals for noise control, ectopic band removal, application of a bandpass filter, and signal saving based on sleep staging. Additional artifact removal and signal preprocessing were conducted using the NeuroKit2 Python package [18]. Peak detection was performed using multiple detectors, and the top-performing detector, the Pan-Tompkins algorithm was selected for further analysis. QRS complexes were detected without differentiating by sleep stage, and signals were segmented into 5-minute epochs with a 30-second overlap. The segments were analyzed and total of 91 HRV features were extracted. These variables were then compared, and 3 to 10 fold cross validation was conducted (Fig. 2). The list of 91 HRV features used in the analysis is presented in Supplementary Table 1 (in the online-only Data Supplement).

Several machine learning (ML) classifiers were employed, including Support Vector Machine (SVM), Decision Tree (DT), Random Forest (RF), K-Nearest Neighbor (KNN), AdaBoost, Logistic Regression (LR), and Arithmetic Neural Network (ANN). Classification was conducted in a stepwise manner, with comparisons made between different classes (Fig. 2).

Statistical Analysis

Demographic data were compared using a one-way analysis of variance for normally distributed variables and Kruskal-Wallis rank sum test for non-normally distributed variables Fisher's exact test was used to analyze categorical variables. All statistical analyses were conducted using R software (version 4.4.1; R Foundation for Statistical Computing). A two-sided p-values of <0.05 was considered statistically significant.

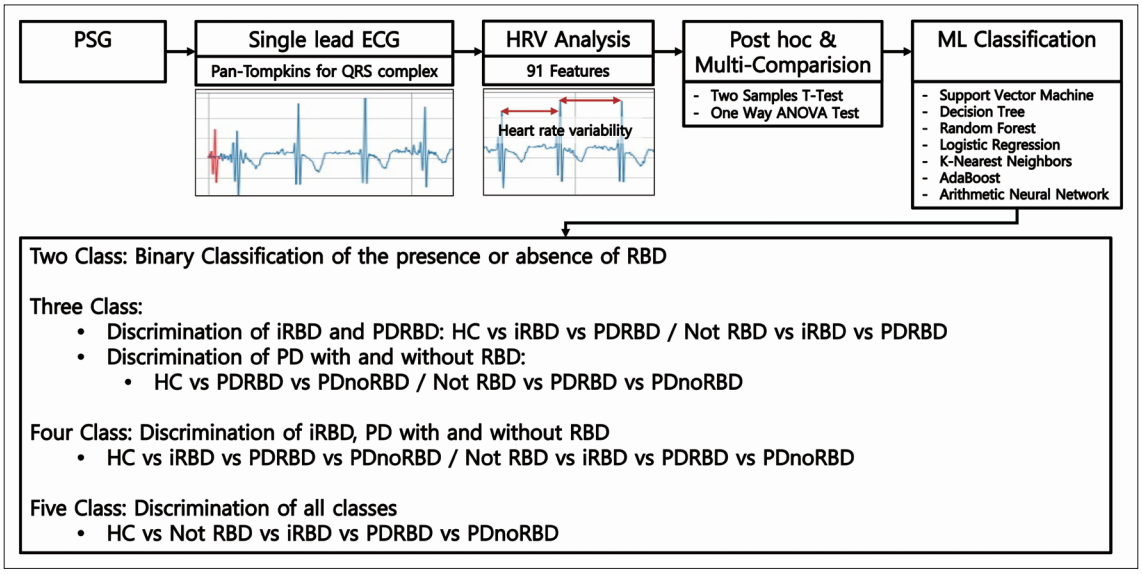

Fig. 2. Diagram of ECG signal processing and analysis process. PSG, polysomnography; ECG, electrocardiogram; HRV, heart rate variability; ML, machine learning; QRS, QRS complex; ANOVA, analysis of variance; REM, rapid eye movement; RBD, REM sleep behavior disorder; iRBD, idiopathic RBD; PDRBD, Parkinson's disease with REM sleep behavior disorder; PDnoRBD, Parkinson's disease without REM sleep behavior disorder; HC, healthy control.

Ethical Approval

The present study was approved by the Institutional Review Board of Severance Hospital, Yonsei University (approval no. 4-2022-0875). The research was conducted in accordance with the principles of the Declaration of Helsinki. Informed consent was waived due to the retrospective design of the study.

RESULTS

Participants

A total of 183 datasets from 161 individuals who had undergone both PSG and ^{18}F-FP-CIT PET between January 1, 2010 and December 31, 2021, were identified through an internal database search. Of these, 94 participants were excluded. After a second review of the medical records, individuals diagnosed with MSA, PDD, DLB, or discordant final diagnoses—such as SWEDD or IPD diagnosed despite normal dopamine PET results—were excluded. This process resulted in 4 participants in the iRBD (PET-negative, RBD-positive) group. For the MC (PET-negative, RBD-negative), PDRBD (PET-positive, RBD-positive), and PDnoRBD (PET-positive, RBD-negative) groups, manual matching based on age, sex, and OSA severity yielded 9, 9, and 8 participants, respectively. The process and specific diagnoses for each group are detailed in Fig. 1.

Demographic Data

There were no significant differences in sex, age at the time of PSG, age at the time of PET, or the interval between PET and PSG among the groups. However, significant differences were observed in DEB between the groups. Most individuals in the iRBD and PDRBD groups exhibited DEB except for one in iRBD group, whereas only half of those without RBD reported DEB.

Regarding PSG parameters, no significant differences were noted in the AHI or OSA severity across the four groups; however, the PDRBD group demonstrated a lower median AHI. As expected, RWA was present only in the iRBD and PDRBD groups, consistent with the diagnostic criteria for RBD. Phenoconversion had not occurred during the interval period between PSG and PET in any participants. The HC group was significantly younger (29.73±5.38 years, mean±standard deviation; $p<0.001$) and had a lower AHI (2.1 [1.7], median [IQR]; $p<0.001$) compared to the other groups (Table 1). Because the number of individuals varied across groups, the total PSG recording time as well as the durations of REM and non-rapid eye movement (NREM) sleep differed between groups (Table 2).

Comparison of HRV Features

There were significant differences in HRV parameters among the five groups, including HC, across time-domain measures (mean of normal-to-normal [NN] intervals, standard deviation of NN intervals), frequency-domain measures (very low frequency [LF] power, low frequency power, high frequency [HF] power, total power), and Poincaré plot analysis. The comparison of selected HRV features—chosen from 91 total features—is presented in Supplementary Table 2 (in the online-only Data Supplement), and the corresponding post hoc analysis is provided in Supplementary Table 3 (in the online-only Data Supplement).

Classification Performance by ML Algorithms

The binary classification to discriminate the presence of RBD using HRV features across various ML algorithms—SVM, DT,

Table 1. Demographics and polysomnography features of the four groups

	iRBD (n=4)	MC (n=9)	PDRBD (n=9)	PDnoRBD (n=8)	Total (n=30)	p-value
Sex						0.637
Male	2 (50.0)	5 (55.6)	7 (77.8)	6 (75.0)	20 (66.7)	
Female	2 (50.0)	4 (44.4)	2 (22.2)	2 (25.0)	10 (33.3)	
DEB						0.034
No	1 (25.0)	5 (55.6)	0 (0.0)	4 (50.0)	10 (33.3)	
Yes	3 (75.0)	4 (44.4)	9 (100.0)	4 (50.0)	20 (66.7)	
PET-PSG interval (day)	114.0 [289.0]	253.0 [1,426.0]	335.0 [390.0]	808.0 [1,174.0]	330.0 [1,063.5]	0.367
PET_age (yr)	61.8±13.1	67.0±10.4	66.0±8.5	65.4±12.8	65.6±10.5	0.882
PSG_age (yr)	61.3±13.1	66.3±8.9	65.6±7.5	64.1±10.0	64.8±9.0	0.822
AHI	31.6 [18.0]	19.9 [7.9]	15.2 [28.7]	30.8 [24.4]	25.5 [27.5]	0.863
OSA_severity						0.242
None	0 (0.0)	0 (0.0)	3 (33.3)	2 (25.0)	5 (16.7)	
Mild	0 (0.0)	1 (11.1)	1 (11.1)	0 (0.0)	2 (6.7)	
Moderate	2 (50.0)	6 (66.7)	1 (11.1)	2 (25.0)	11 (36.7)	
Severe	2 (50.0)	2 (22.2)	4 (44.4)	4 (50.0)	12 (40.0)	
Proportion of epochs with RWA/ total REM epochs (%)	36.6 [21.3]	0.0 [0p.0]	22.1 [33.1]	0.0 [0.0]	0.0 [21.1]	<0.001

Fisher's exact test, Kruskal-Wallis rank sum test, and one-way analysis of variance were used as appropriate. Data are presented as the mean±standard deviation, median [interquartile range], or number (%).
DEB, dream-enactment behaviors; PET, positron emission tomography; PSG, polysomnography; AHI, Apnea-Hypopnea Index; OSA, obstructive sleep apnea; REM, rapid eye movement; RWA, REM sleep without atonia; iRBD, idiopathic REM sleep behavior disorder; MC, matched control; PDRBD, Parkinson's disease with REM sleep behavior disorder; PDnoRBD, Parkinson's disease without REM sleep behavior disorder.

Table 2. Duration of REM and NREM sleep in each group

Group	Time of stage_N (min)	Time of stage_R (min)	Number of persons in each group
HC	4,793.5	964.5	15
iRBD	1,454.5	274.0	8
PDRBD	2,303.4	502.0	9
MC	2,591.0	432.5	9
PDnoRBD	1,932.4	237.0	4

REM, rapid eye movement; NREM, non-rapid eye movement; HC, healthy control; PDnoRBD, Parkinson's disease without REM sleep behavior disorder; PDRBD, Parkinson's disease with REM sleep behavior disorder; MC, matched control; iRBD, idiopathic REM sleep behavior disorder.

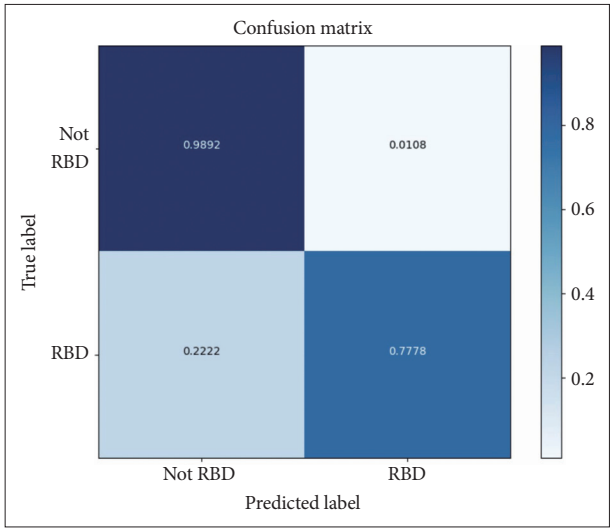

Fig. 3. Confusion matrix of Support Vector Machine for binary classification of presence of rapid eye movement sleep behavior disorder (RBD).

RF, LR, KNN, AdaBoost, and ANN—showed that SVM achieved the best performance, with accuracy, sensitivity, precision, and F1-score of 0.95, 0.95, 0.95, and 0.95, respectively (Fig. 3).

In the three-class classification to discriminate iRBD and PD, SVM achieved the best performance when classifying HC, iRBD, and PDRBD. However, approximately half of the iRBD cases were misclassified. When classifying MC, iRBD, and PDRBD, SVM again demonstrated the highest performance. For distinguishing PD with and without RBD—specifically classifying HC, PDRBD, and PDnoRBD—RF, LR, and ANN achieved the best results; however, PDnoRBD cases were frequently misclassified as HC. In the classification of MC, PDRBD, and PDnoRBD, RF and KNN showed the highest performance (Table 3 and Fig. 4).

In the four-class classification to discriminate among HC, iRBD, PDRBD, and PDnoRBD, ANN demonstrated the best performance. PDRBD and HC were well classified, whereas classifi-

Table 3. Machine learning results for 3 class classifications

Model	HC vs. iRBD vs. PDRBD				MC vs. iRBD vs. PDRBD				HC vs. PDRBD vs. PDnoRBD				MC vs. PDRBD vs. PDnoRBD			
	Accuracy	Recall	Precision	F1-score	Accuracy	Recall	Precision	F1-score	Accuracy	Recall	Precision	F1-score	Accuracy	Recall	Precision	F1-score
SVM	0.95	0.95	0.95	0.95	0.91	0.91	0.91	0.91	0.97	0.96	0.97	0.96	0.94	0.94	0.95	0.93
DT	0.91	0.91	0.91	0.91	0.83	0.83	0.86	0.84	0.96	0.96	0.96	0.97	0.94	0.94	0.96	0.95
RF	0.91	0.91	0.91	0.90	0.85	0.85	0.87	0.85	0.97	0.97	0.98	0.97	0.97	0.97	0.99	0.98
LR	0.89	0.89	0.89	0.88	0.89	0.89	0.89	0.89	0.97	0.97	0.98	0.97	0.94	0.94	0.95	0.94
KNN	0.93	0.93	0.92	0.92	0.78	0.78	0.81	0.78	0.96	0.96	0.96	0.95	0.97	0.97	0.97	0.97
AB	0.90	0.90	0.90	0.90	0.76	0.76	0.85	0.77	0.91	0.91	0.91	0.90	0.89	0.89	0.90	0.88
ANN	0.93	0.93	0.93	0.93	0.89	0.89	0.89	0.89	0.97	0.97	0.98	0.97	0.92	0.92	0.93	0.92

SVM, Support Vector Machine; DT, Decision Tree; RF, Random Forest; LR, Logistic Regression; KNN, K-Nearest Neighbor; AB, AdaBoost; ANN, Arithmetic Neural Network; HC, healthy control; REM, rapid eye movement; iRBD, idiopathic REM sleep behavior disorder; PDRBD, Parkinson's disease with REM sleep behavior disorder; PDnoRBD, Parkinson's disease without REM sleep behavior disorder; MC, matched control.

cation performance for iRBD and PDnoRBD was lower. In the classification of MC, iRBD, PDRBD, and PDnoRBD, RF achieved the highest performance. MC, iRBD, and PDRBD were classified with relatively high accuracy, while PDnoRBD again showed lower classification performance (Table 4 and Fig. 5).

Finally, in the five-class classification of HC, MC, iRBD, PDRBD, and PDnoRBD, SVM demonstrated the best overall performance. Classification accuracy was high for PDRBD, MC, and HC; however, performance for iRBD was lower, and all PDnoRBD cases were misclassified as HC (Table 4 and Fig. 6).

DISCUSSION

The main findings of the present study were as follows: Based on HRV features derived from PSG-ECG data, the ML classifiers successfully classified: 1) the presence of RBD compared to controls, 2) iRBD and PDRBD compared to controls, 3) PDRBD or PDnoRBD compared to controls, and 4) iRBD, PDRBD, and PDnoRBD compared to controls.

Our study aimed to classify the presence of RBD and differentiate between iRBD and PDRBD using ECG, specifically HRV. Autonomic dysfunction is frequently reported in alpha-synucleinopathies. Evidence suggests that dysautonomia precedes both motor and non-motor symptoms of PD. This has been attributed to the ascending pathology of alpha-synuclein and the gut-brain axis, where pathology spreads from the viscera to the brainstem via the vagus nerve. As a critical component of the autonomic nervous system, the vagus nerve plays a key role, and its dysfunction leads to various dysautonomic symptoms [2,10,13,19,20]. The cardiac rhythm is partially controlled by the vagus nerve and regulated through the balance of the sympathetic and parasympathetic nervous systems. Cardiovagal functions have traditionally been assessed using autonomic function tests [21]. HRV refers to fluctuations in heartbeat intervals and variations in the time between consecutive heartbeats, reflecting the interaction between the sympathetic and parasympathetic systems. The cardio-accelerating centers are innervated by cardiac sympathetic nerves, including fibers from the cervicothoracic ganglion and the vagus nerve. Normal cardiac variability depends on the stimulation of the sinoatrial node by these pathways, which can be assessed through HRV analysis. Consequently, HRV analysis serves as a valuable tool for evaluating autonomic dysfunction. Evidence of dysautonomia and cardiac dysfunction in RBD has been reported. Autonomic dysfunction in iRBD patients was intermediate between that of controls and PD patients [22]. iRBD patients do not exhibit the typical physiological parasympathetic withdrawal and sympathetic dominance observed during the transition from NREM to REM sleep [22]. REM-related cardiac and respiratory responses were found to be absent in iRBD [23]. A study by Postuma et al. [12] used ECG signals from PSG and found that abnormal cardiac auto-

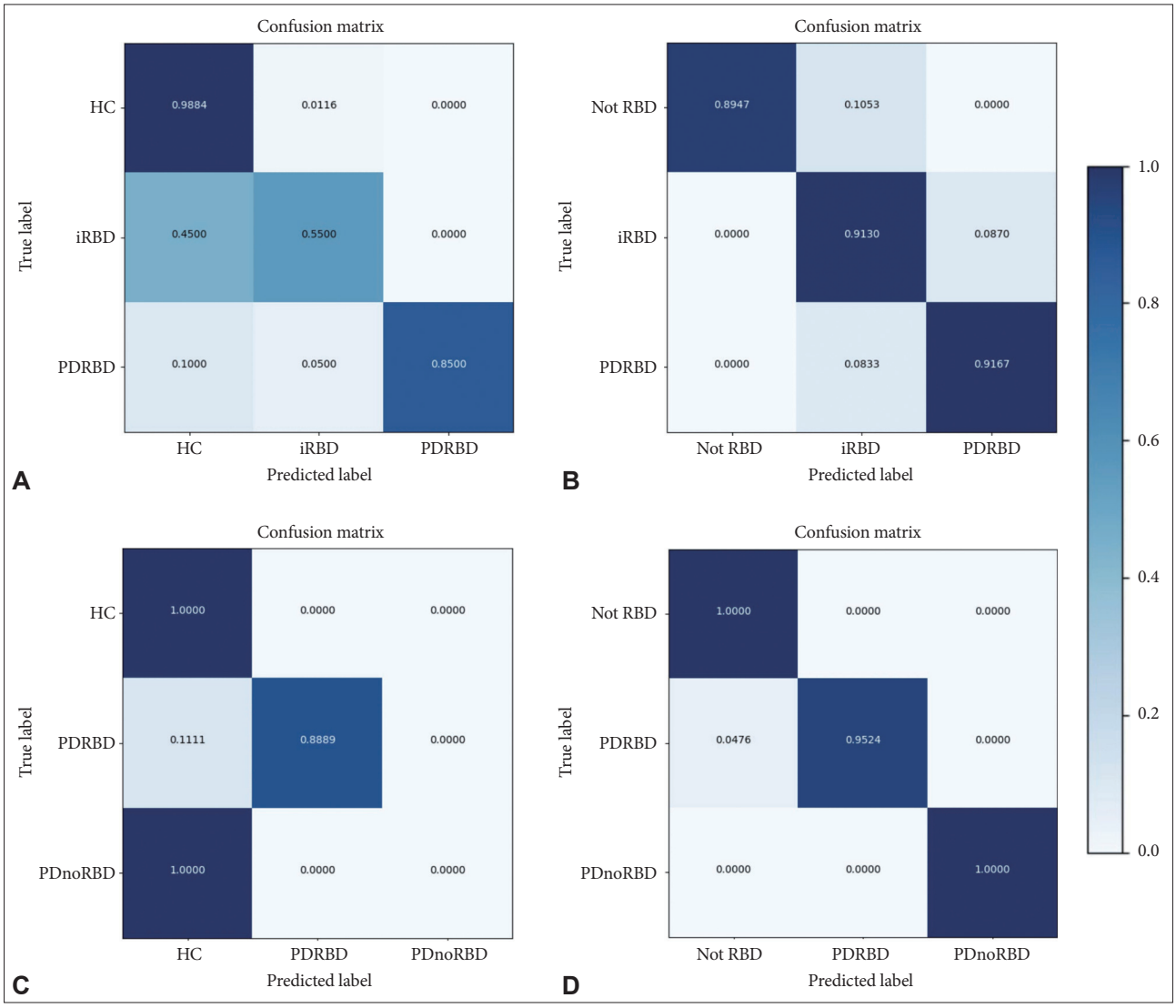

Fig. 4. Confusion matrix of 3 class classifications by machine learning methods. A: HC vs. iRBD vs. PDRBD, SVM. B: MC vs. iRBD vs. PDRBD, SVM. C: HC vs. PDRBD vs. PDnoRBD, Random Forest. D: MC vs. PDRBD vs. PDnoRBD, K-Nearest Neighbor. HC, healthy control; iRBD, idiopathic rapid eye movement sleep behavior disorder; PDRBD, Parkinson's disease with rapid eye movement sleep behavior disorder; PDnoRBD, Parkinson's disease without rapid eye movement sleep behavior disorder; SVM, Support Vector Machine; MC, matched control.

nomic measures were evident in PDRBD but not in PDnoRBD when compared to controls, suggesting that RBD, rather than PD, is associated with cardiac autonomic denervation. The findings in our study are also consistent with PDnoRBD frequently being misclassified as HC. However, interpretation is limited by the fact that MC, which was intended to serve as a control group, was well differentiated from HC.

The notion that RBD is more closely associated with autonomic dysfunction is further supported by a study evaluating ^{123}I-metaiodobenzylguanidine uptake, which was found to be more markedly reduced in iRBD than in early-stage PD patients. This suggests that cardiac autonomic dysfunction is more closely related to RBD itself rather than being a preclinical sign of neurodegenerative disease [16]. Another study reported reduced tonic and phasic HRV during sleep in RBD patients, suggesting that autonomic evaluation during sleep may detect impairments earlier than traditional autonomic testing conducted during wakefulness [24]. These findings support the rationale for evaluating RBD using HRV derived from ECG of PSG.

Our study successfully discriminated RBD from controls using ML methods and HRV features derived from ECG. According to the ICSD-3 criteria [4], the diagnosis of RBD requires repeated dream enactment behaviors and PSG-documented RWA. The assessment of RWA during PSG does not incorporate ECG signals. However, given the close relationship between cardiac autonomic dysfunction and RBD [12], predicting RBD using ECG may be a reasonable approach. Additionally, performing PSG requires significant resources, and accessing a hospital for

Table 4. Machine learning results for 4 and 5 class classifications

Model	HC vs. iRBD vs. PDRBD vs. PDnoRBD				MC vs. iRBD vs. PDRBD vs. PDnoRBD				HC vs. MC vs. iRBD vs. PDRBD vs. PDnoRBD			
	Accuracy	Recall	Precision	F1-score	Accuracy	Recall	Precision	F1-score	Accuracy	Recall	Precision	F1-score
SVM	0.87	0.87	0.88	0.85	0.86	0.86	0.87	0.84	0.93	0.93	0.93	0.92
DT	0.86	0.86	0.85	0.84	0.75	0.75	0.80	0.76	0.86	0.86	0.87	0.86
RF	0.87	0.87	0.89	0.85	0.91	0.91	0.92	0.91	0.92	0.92	0.91	0.91
LR	0.87	0.87	0.86	0.84	0.89	0.89	0.90	0.88	0.89	0.89	0.87	0.88
KNN	0.85	0.85	0.83	0.82	0.88	0.88	0.89	0.86	0.90	0.90	0.89	0.89
AB	0.40	0.40	0.76	0.44	0.71	0.71	0.77	0.73	0.81	0.81	0.80	0.77
ANN	0.92	0.92	0.91	0.91	0.86	0.86	0.87	0.86	0.91	0.91	0.91	0.91

SVM, Support Vector Machine; DT, Decision Tree; RF, Random Forest; LR, Logistic Regression; KNN, K-Nearest Neighbor; AB, AdaBoost; ANN, Arithmetic Neural Network; HC, healthy control; REM, rapid eye movement; iRBD, idiopathic REM sleep behavior disorder; PDRBD, Parkinson's disease with REM sleep behavior disorder; PDnoRBD, Parkinson's disease without REM sleep behavior disorder; MC, matched control.

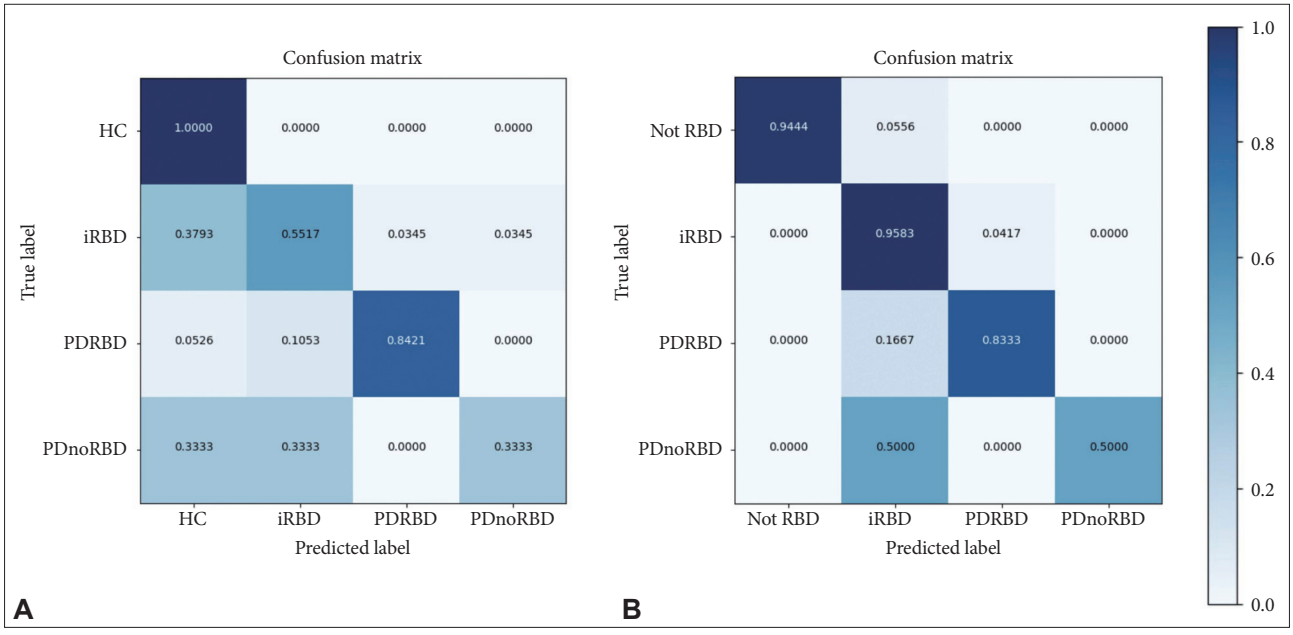

Fig. 5. Confusion matrix of 4 class classification by machine learning methods. A: HC vs. iRBD vs. PDRBD vs. PDnoRBD, Arithmetic Neural Network. B: Matched control vs. iRBD vs. PDRBD vs. PDnoRBD, Random Forest. HC, healthy control; iRBD, idiopathic rapid eye movement sleep behavior disorder; PDRBD, Parkinson's disease with rapid eye movement sleep behavior disorder; PDnoRBD, Parkinson's disease without rapid eye movement sleep behavior disorder.

PSG is more challenging for individuals with parkinsonism or gait disturbances. In contrast, a routine ECG is a simpler procedure that takes less time and can be conducted outside of a sleep laboratory. Although further research is needed to establish the feasibility of predicting RBD from routine ECG, our study using nighttime ECG provides valuable insights for future investigations.

ECG signals have been used to detect periodic limb movements and sleep apnea [5-8]. HRV has previously been used to identify iRBD. In a study of 72 subjects, including 29 with iRBD, PSG-derived HRV was analyzed; unfortunately, none of the HRV components were able to predict the presence of iRBD in the full cohort [25]. However, this study did not utilize ML methods for analysis. Additionally, other studies using PSG-derived signals and ML or DL have successfully classified RBD. Study by Urtnasan et al. [9] used single-lead ECG signals and a deep learning algorithm to classify insomnia, periodic leg movement, RBD, and nocturnal frontal lobe epilepsy. This study differs from ours in that it compared diseases that are not pathophysiologically related. RBD has also been assessed using other signals derived from PSG. A study by Cesari et al. [26] used EEG and EOG signal-derived features and an ensemble of RF to classify the probability of RBD in 107 de novo PD patients. When distinguishing between PDnoRBD and PDRBD, they identified RBD with accuracy, sensitivity, and specificity exceeding 80%. Micro-sleep instability was the most important feature for RBD identifica-

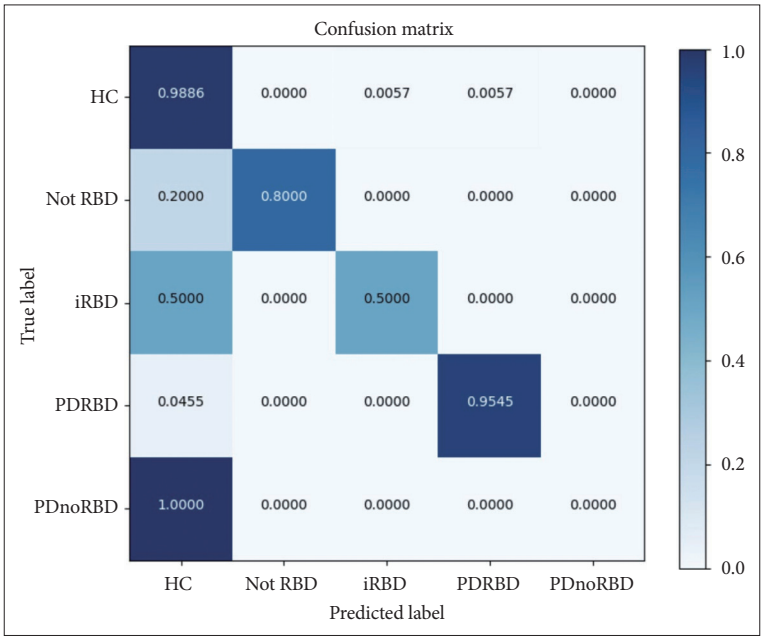

Fig. 6. Confusion matrix of 5 class classification by machine learning methods. HC vs. matched control vs. iRBD vs. PDRBD vs. PDnoRBD, Support Vector Machine. HC, healthy control; iRBD, idiopathic rapid eye movement sleep behavior disorder; PDRBD, Parkinson's disease with rapid eye movement sleep behavior disorder; PDnoRBD, Parkinson's disease without rapid eye movement sleep behavior disorder.

tion. Among PD patients with REM behavioral events, those with significantly higher RBD probability scores developed definite RBD after 2 years. Other studies have used EMG signals from PSG along with ML or deep neural networks to detect RWA or RBD [27,28].

Other sleep disorders may also disrupt cardiovascular autonomic function, potentially confounding HRV. A bidirectional association exists between sleep disorders and autonomic dysfunction, independent of their relationship with RBD [22]. Additionally, disorders such as sleep apnea, insomnia, restless legs syndrome (RLS), and narcolepsy influence the autonomic nervous system. RBD may be present in narcolepsy, while sleep apnea and insomnia can mimic, coexist with, or exacerbate RBD [29]. In our study, we attempted to match OSA severity between groups to minimize confounding factors and address this issue. While no participants had narcolepsy, the presence of RLS was not assessed.

As the presence of RBD strongly suggests conversion to alpha-synucleinopathy [1], diagnosing RBD is a major concern. However, not all individuals with RBD develop dementia or parkinsonism, highlighting the importance of predicting phenoconversion from iRBD to overt alpha-synucleinopathy as a key issue for RBD patients.

There were no phenoconverted patients in our study; however, we successfully discriminated controls from iRBD and PD, suggesting significant differences between iRBD and PDRBD. In a study by McCarter et al. [13], among 18 patients followed for 3 years, 12 (67%) underwent phenoconversion—6 to PD and 6 to DLB. Of these, 15 exhibited at least mild autonomic dysfunction. Those who developed DLB had significantly higher total and cardiovagal composite autonomic severity scores compared to those who developed PD. Autonomic dysfunction is widely observed in iRBD patients, and more severe baseline cardiovagal autonomic dysfunction in iRBD has been associated with phenoconversion to DLB but not PD. Findings from this study and our study suggest that while a prospective study is needed to establish a predictive mechanism for phenoconversion, HRV signals reflecting cardiovagal function may indicate greater dysautonomia in iRBD patients and provide foundational evidence for future research.

The presence of RBD in patients with overt PD is clinically significant; however, not all PD patients exhibit RBD. This distinction is currently explained by the brain-first and body-first subtypes of alpha-synucleinopathy. PD symptoms emerge when pathological changes reach the basal ganglia and cortex. Regardless of the route through which pathology reaches the brainstem, RBD manifests; however, it is more prevalent and frequent in the body-first subtype. This subtype, which is hypothesized to originate from pathology ascending via the vagus nerve, is also associated with more pronounced autonomic dysfunction and more severe symptoms. Previous studies have demonstrated a strong association between RBD and autonomic dysfunction. For example, orthostatic hypotension has been linked to RBD, with studies showing greater systolic blood pressure changes during orthostasis in affected individuals [30]. More importantly, HRV differences between PDRBD and PDnoRBD have been reported [15]. Nocturnal LF and HF spectral power values were significantly higher in PDRBD than in PDnoRBD ($p<0.001$ and $p=0.004$), and these values were also higher at night than during the day in PDRBD. Our study successfully classified PDRBD and

PDnoRBD, as well as iRBD and controls, using ML techniques with single-lead ECG-derived HRV features. Given that PDRBD is associated with more severe symptoms than PDnoRBD, early discrimination may help predict prognosis and guide tailored treatment strategies. While further prospective studies are needed to confirm these findings, our study suggests that progression to PDRBD or PDnoRBD may be predicted, potentially allowing for early intervention and personalized disease management strategies in the future.

This study has several limitations. First, due to its retrospective nature, the actual clinical status of participants at the time of PSG and PET remains uncertain. Classification into iRBD, PDRBD, or PDnoRBD was based on review of medical records, raising the possibility that some participants classified as iRBD may have been in the early stages of IPD or other parkinsonian syndromes. However, to enhance diagnostic accuracy, we cross-referenced PSG, EMR, and PET results and excluded ambiguous cases to minimize potential misclassification. Furthermore, no phenoconversion was observed during the interval between PSG and PET, supporting the stability of our classification.

Second, the diagnosis of RBD was based on PSG-confirmed repeated dream enactment behaviors and the loss of RWA, following ICSD-3 criteria. However, different AASM criteria were applied over the years, reflecting changes in scoring standards at the time of PSG acquisition. This inconsistency in diagnostic criteria may have introduced variability in the classification of RBD cases. Future studies should apply updated PSG scoring criteria to re-evaluate existing data and ensure consistency in diagnosis.

Third, the selection of the HC group presents a limitation. Although categorized as HC, these participants were not entirely asymptomatic; they exhibited symptoms despite not meeting the criteria for sleep disorders such as OSA or RBD. Additionally, differences in age and OSA severity between the HC group and other groups could introduce confounding effects when using HC as a control. However, to mitigate this issue, we included an additional control group, MC, for comparison. Our algorithm successfully predicted RBD regardless of whether MC or HC was used as the control group.

Fourth, although we systematically classified RBD subtypes, the study population was relatively small, particularly in the iRBD group. Indeed, in some analyses, classification of iRBD showed lower accuracy than other groups. Also, the limited number of participants in each group may affect the generalizability of our findings. iRBD is known to exhibit decreased ^{18}F-FP-CIT PET uptake prior to an IPD diagnosis. However, in this study, we excluded cases with abnormal PET findings if definite parkinsonism was not present. While this may have resulted in a smaller number of iRBD cases, and consequently in shorter PSG time and imbalanced data, we aimed to exclude ambiguous cases given the retrospective nature of the study and the potential impact of misclassification on our results. Future studies with larger sample sizes are needed to validate our results. Additionally, we selected patients with similar OSA severity across the groups; however, this process was not conducted using formal methods such as propensity score matching, which may introduce potential bias. Nevertheless, demographic characteristics did not differ significantly between groups, suggesting that the impact of this limitation is likely minimal.

Fifth, although we demonstrated classification feasibility using total HRV features, this approach inevitably lacks specificity given the variability across sleep stages, which may be a critical confounder in this study. By not differentiating sleep stages, our analysis may have overlooked meaningful intra-sleep variability and potentially higher classification accuracy. However, this study was intended to be exploratory, focusing on the feasibility of using HRV features to classify iRBD and PDRBD. Additionally, considering future applications such as daytime routine ECG or Holter monitoring—which do not currently incorporate sleep staging—we aimed to evaluate the potential of a more generalized approach. Still, we acknowledge that this limits both the validity and potential clinical applicability of our findings. Future prospective studies with well-curated, balanced datasets should incorporate sleep-stage-specific HRV features to assess their added value in classification performance.

Lastly, we did not investigate medications taken by participants. While we excluded individuals with known AF and pacemaker insertion, minor arrhythmias such as sinus arrhythmia and first-degree atrioventricular block were included. These conditions are typically not treated, but some participants may have been taking medications for arrhythmias. Additionally, participants with tremor may have been prescribed beta blockers. Medications for DEBs are usually withheld for two weeks prior to PSG, but we could not confirm whether this protocol was followed. In participants with PD, dopaminergic medications were likely continued. These medications may have interfered with HRV. These factors represent limitations of our study. However, in a retrospective design, controlling for medication use and systematically investigating their impact is inherently challenging. A prospective study with standardized medication control would provide more robust and reliable results.

Despite these limitations, our study offers new insights into the early recognition of RBD using ECG-derived HRV features and ML classification. Future prospective studies with larger cohorts are needed to further validate our findings and enhance predictive models for phenoconversion to overt α-synucleinopathy.

In conclusion, using ML methods, HRV features from single-lead ECG obtained during PSG successfully classified iRBD, PDRBD, and PDnoRBD. While our study provides valuable insights into early RBD recognition, larger prospective studies are required to validate ECG-derived markers for predicting RBD and phenoconversion, facilitating earlier intervention and risk stratification.

Supplementary Materials

The online-only Data Supplement is available with this article at https://doi.org/10.17241/smr.2025.02831.

Availability of Data and Material

As this was a retrospective study, informed consent from participants was not obtained. Therefore, only limited data can be shared by the corresponding author upon reasonable request.

Author Contributions

Conceptualization: Wonwoo Lee. Data curation: all authors. Formal analysis: Hye Jeong Lee, Ju Hyuck Han, Jonguk Park, Wonwoo Lee. Funding acquisition: Wonwoo Lee. Investigation: all authors. Methodology: Ju Hyuck Han, Jonguk Park, Wonwoo Lee. Project administration: Wonwoo Lee. Supervision: Wonwoo Lee. Validation: all authors. Writing—original draft: Hye Jeong Lee, Ju Hyuck Han, Jonguk Park, Wonwoo Lee. Writing—review & editing: all authors.

Conflicts of Interest

Wonwoo Lee was involved as a site investigator in a multicenter trial sponsored by Eli Lilly and Co., WhanIn Pharm Co. Ltd., and Handok-Teva. He has received lecture honoraria from Abbott and SK chemical in the past 24 months. The other authors have nothing to declare.

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