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The Many Faces of REM Sleep Behavior Disorder. Providing Evidence for a New Lexicon

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ABSTRACT

Background: People with idiopathic/isolated REM sleep behavior disorder (iRBD) are highly heterogeneous, showing mild motor, cognitive, and dysautonomia symptoms. The aim of this study is to unveil the clinical heterogeneity of iRBD with a specific reference to overlapping features with prodromal Parkinson's disease (pPD) and prodromal dementia with Lewy bodies (pDLB) labels.

Methods: People with a polysomnography-confirmed diagnosis of iRBD were enrolled and followed over time. At baseline, pPD and pDLB criteria were assessed.

Results: Among the 285 iRBD people (68.2 ± 7.6 years, 81% males), due to additional signs or symptoms, 49.8% fulfilled pPD criteria only, 5.6% pDLB criteria only, and 14.4% subjects fulfilled both pPD and pDLB criteria. Conversely, about one third of iRBD people (30.2%) did not meet either pPD or pDLB criteria. At follow-up (40.6 ± 43.6 months), 28.8% subjects phenoconverted, developing PD (56.1%), DLB (39%), or multiple system atrophy (4.9%). Subjects with iRBD fulfilling either pPD or pDLB criteria, or both, have an increased risk of phenoconversion (adjusted hazard ratio, aHR 2.34, 95% confidence interval, CI 1.24–4.41). On the opposite, subjects not fulfilling prodromal criteria have a significantly reduced short-term phenoconversion likelihood (aHR 0.43, 95% CI 0.23–0.81). Notably, pPD and pDLB criteria did not predict PD and DLB diagnoses, respectively.

Conclusions: People with iRBD are highly heterogeneous, and the presence of other concomitant signs and symptoms is frequent, leading to faster phenoconversion. Thus, the terms idiopathic and isolated may be poorly appropriate and possibly even confounding. These results pave the way to a more appropriate new lexicon for people with RBD.

1 | Introduction

REM sleep behavior disorder (RBD) is a parasomnia characterized by dream-enacting behaviors and the loss of physiological muscle tone during REM sleep [1]. RBD without overt neurological signs, such as dementia or Parkinsonism, has historically been defined as idiopathic (iRBD). Subsequently, the label "clinically isolated", which would apply to RBD patients who do not have overt motor or cognitive signs or symptoms, has been proposed as a replacement for the term "idiopathic" [2]. Nevertheless, at the time of diagnosis, most iRBD patients show mild motor symptoms, mild cognitive impairment (MCI), autonomic and olfaction dysfunctions, and neuroimaging abnormalities (mostly abnormal presynaptic dopaminergic imaging, typically on SPECT, i.e., DaT-SPECT), which are suggestive of incipient alpha-synucleinopathy [3–5]. Indeed, the vast majority of iRBD patients will eventually receive a clinical diagnosis of Parkinson's disease (PD) or dementia with Lewy bodies (DLB), and a minority of multiple system atrophy (MSA) [5]. Research criteria for prodromal PD (pPD) [6] and prodromal DLB (pDLB) [7] were defined based on the acknowledgment that these disorders have a long prodromal stage before the emergence of overt Parkinsonism and/or dementia. In this context, the presence of polysomnography-confirmed RBD is among the strongest indicators of both pPD and pDLB. Following this mounting evidence, a new framework on the alpha-synucleinopathy spectrum is being proposed [8, 9], suggesting that the prodromal and overt stages should no longer be clearly distinct. According to this framework, the presence of polysomnography-confirmed RBD is associated with an underlying alpha-synucleinopathy with the same likelihood of clinical demonstration of overt Parkinsonism, dementia, and neurogenic orthostatic hypotension [8, 9]. Indeed, pathological alpha-synuclein is found in the cerebrospinal fluid and skin in up to 97% of living people with "idiopathic/isolated" RBD [10, 11]. This finding, along with the concomitant, albeit subtle, signs and/or symptoms likely associated with neurodegeneration found in most iRBD patients, raises the question of whether the labels "idiopathic" and "clinically isolated" remain adequate. As a further complication, RBD may be due to other disorders, such as narcolepsy, autoimmune encephalitis, and brainstem lesions, in a significant proportion of people [2]. Thus, a new lexicon on RBD may be envisioned by switching from a descriptive framework to a more biology-driven one. Thus, better understanding and characterizing the heterogeneity of people with RBD is essential.

The aim of the present study was to provide a snapshot of baseline features in a large group of people diagnosed with idiopathic/isolated RBD, revealing their clinical heterogeneity and overlap with pPD and pDLB labels, as well as their longitudinal trajectories.

2 | Methods

People with a polysomnography-confirmed diagnosis of RBD were consecutively enrolled at four Italian centers (Bologna, Cagliari, Genoa and Pavia) within the FarPresto consortium [12, 13]. All patients were diagnosed with iRBD according to international criteria [14].

Baseline clinical assessment included collection of the (i) first medical complaint, which is the clinical reason that led people to seek medical attention; (ii) personal and familiar history; (iii) physical and neurological examination, including the Movement Disorders Society Unified Parkinson's Disease Rating Scale motor section (MDS-UPDRS-III) to investigate motor symptoms; (iv) the Mini-Mental State Examination (MMSE) as a global cognition measure; (v) a comprehensive neuropsychological assessment to assess the presence of mild cognitive impairment (MCI) [15] or dementia; and (vi) the Sniffin's stick test or the UPSIT smell test for hyposmia. Details can be found in the FarPresto project description [13]. Moreover, a subgroup of patients underwent baseline [^{123}I]FP-CIT-SPECT (DaT-SPECT) as a measure of presynaptic dopaminergic degeneration. DaT-SPECT scans were classified based on a visual scale by expert nuclear medicine physicians as follows: (i) normal, (ii) unilateral putaminal reduced uptake, (iii) bilateral putaminal reduced uptake, and (iv) diffuse reduced uptake. Details can be found in previous FarPresto publications [12, 13].

Based on additional signs and/or symptoms beyond RBD, the current criteria for the diagnosis of pPD [6] and pDLB [7] were retrospectively applied by two expert neurologists who critically reviewed the clinical reports. In detail, for pPD diagnosis, all available clinical information was carefully assessed, and the pPD probability was computed by using the MDS web portal for pPD research (www.movementdisorders.org/pdcalculator) and by applying an 80% threshold. The pDLB diagnosis may be more open to interpretation. However, according to current criteria [7], probable pDLB with cognitive onset can be diagnosed in the presence of MCI, as an essential criterion, and of RBD (core clinical feature) with polysomnographic confirmation of REM sleep without atonia (diagnostic biomarker). In our sample, all iRBD patients were polysomnography-confirmed. Thus, the concomitant presence of MCI is sufficient to fulfill the diagnosis of pDLB.

Thus, all the subjects were labeled (i) neither pPD nor pDLB (i.e., clinically isolated RBD), (ii) pPD only, (iii) pDLB only, or (iv) both pPD and pDLB. We chose not to use the prodromal MSA (pMSA) criteria [16] because of the very low phenoconversion rate into MSA and because of substantial overlap between the pMSA criteria with pPD criteria and the pDLB criteria (i.e., all people with pPD/pDLB without hyposmia fulfill the pMSA criteria).

Clinical follow-up was conducted every 6–12 months to investigate the fulfillment of clinically overt PD [17], DLB [18] or MSA [16] diagnosis.

All participants signed an informed consent form in compliance with the Helsinki Declaration of 1975. Ethics approval was obtained from the local institutional boards of all the participating centers, and the study was also approved by the institutional board of the coordinating center.

3 | Statistical Analysis

As a first descriptive step, all baseline and follow-up variables were compared between the four groups of prodromal diagnoses (i.e., neither pPD nor pDLB, pPD only, pDLB only, and both pPD and pDLB). Univariate analysis of variance (ANOVA) was

used for continuous variables. The chi-squared test was used for categorical variables.

Kaplan–Meier survival analysis was first applied, and the hazard ratio (HR) was subsequently calculated with a Cox regression analysis for each variable. Age, sex, and center were used as covariates in the analysis to compute the adjusted HR (aHR). The survival time was considered the time (in months) from the baseline visit to the last follow-up visit for nonconverter patients and to the time of diagnosis of overt alpha-synucleinopathy for converter patients.

Statistical analysis was performed using R code implemented in BlueSky Statistics software (BlueSky Statistics LLC, Chicago, IL, USA).

4 | Results

We enrolled 285 consecutive people with a polysomnography-confirmed diagnosis of iRBD. The main clinical and demographic characteristics of the enrolled subjects are summarized in Table 1. A comprehensive neuropsychological assessment, which can define the presence of MCI, was available for 182 (63.9%) iRBD patients, whereas 225 (79%) patients underwent baseline DaT-SPECT.

In terms of the prodromal diagnosis (Figure 1), 183 (64.2%) iRBD patients fulfilled the pPD criteria, and 57 (20.0%) fulfilled the pDLB criteria, with a partial overlap between the two prodromal diagnoses. Specifically, 49.8% fulfilled the pPD criteria only, 5.6% fulfilled the pDLB criteria only, and 14.4%

TABLE 1 | Clinical and demographic characteristics of iRBD people.

	iRBD people ($n = 285$)
Sex, males	81.1%
Education, years	10.0 ± 4.3 [8]
Age, years	68.2 ± 7.6 [69]
RBD duration prior diagnosis, months	61.4 ± 51.4 [49]
MDS-UPDRS-III	2.7 ± 2.9 [2]
MMSE	27.4 ± 2.4 [28]
MCI[a]	31.3%
DaT-SPECT[a]	
Normal	56%
Unilateral putaminal alteration	16.4%
Bilateral putaminal alteration	22.7%
Diffuse alteration	4.9%
Hyposmia[a]	46.2%
First medical complaint	
Dream-enacting behaviors	84.2%
Motor symptoms	1.4%
Cognitive symptoms	4.2%
Other sleep disorders	7.7%
Other	2.5%
Follow-up time, months	40.6 ± 43.6 [28]
Phenoconverted	28.8%
Phenoconversion diagnosis	
PD	56.1%
DLB	39%
MSA	4.9%

Note: Continuous variables are shown as mean ± standard deviation [median]. Categorical variables are shown as percentage.
Abbreviations: DaT, dopamine transporter; DLB, dementia with Lewy bodies; MCI, mild cognitive impairment; MDS-UPDRS-III, movement disorder society unified Parkinson's disease rating scale motor section; MMSE, mini mental state examination; MSA, multiple system atrophy; PD, Parkinson's disease.
[a]MCI assessment was available in 182/285 (64%) subjects; DaT-SPECT was available in 225/285 (79%) subjects; Olfactory assessment was available in 238/285 (84%) subjects.

fulfilled both the pPD and pDLB criteria. Approximately one-third of the iRBD patients (30.2%) did not meet any prodromal criteria.

The main clinical and demographic characteristics of the iRBD patients, according to the prodromal diagnosis, are summarized in Table 2.

People with iRBD fulfilling the pPD and/or pDLB criteria were older, had worse baseline clinical metrics, and had more markedly altered DaT-SPECT imaging data. As expected, the presence of MCI was the strongest indicator of pDLB. Conversely, iRBD patients fulfilling the pPD diagnosis were characterized by a higher rate of abnormal DaT-SPECT, more severe motor signs, and a higher rate of hyposmia. Notably, iRBD patients fulfilling only the pDLB criteria, not the pPD criteria, were characterized by the presence of MCI alone, without other meaningful signs or symptoms.

As anticipated, the most common first medical complaint was dream-enacting behavior (84.2%). However, some patients sought medical attention for either motor or cognitive symptoms but were then referred to the sleep lab because RBD was suspected during the consultation. The first medical complaint was significantly associated with the pPD/pDLB labels ($p = 0.017$), with iRBD patients complaining of motor symptoms having a pPD label more frequently, whereas iRBD patients with cognitive complaints more frequently had the pDLB label, either alone or associated with the concomitant pPD label.

At follow-up, people who fulfilled both the pPD and pDLB criteria had an increased risk of phenoconversion ($p = 0.002$). Specifically, 54% of the people fulfilling both criteria developed Parkinsonism and/or dementia after a median follow-up of 32 months (range 15–56), whereas 23% of the people not fulfilling any prodromal criteria developed Parkinsonism and/or dementia after a median follow-up of 61 months (range 36–95). However, the labels pPD and pDLB were not associated with a specific phenoconversion diagnosis. Indeed, the PD phenoconversion diagnosis was most common among iRBD patients fulfilling the pPD criteria but also among those fulfilling the pDLB criteria.

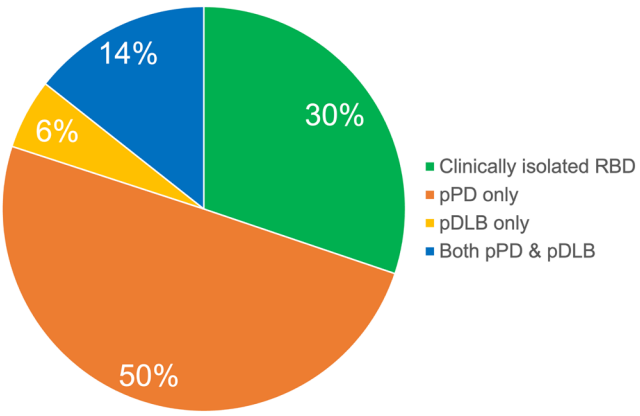

FIGURE 1 | Prodromal criteria in iRBD people. In 14.4% of subjects both pPD and pDLB criteria were met, 5.6% subjects had only the pDLB label, 49.8% subjects had only the pPD label, while 30.2% did not meet any prodromal criteria (i.e., clinically isolated RBD).

Interestingly, iRBD patients with both prodromal labels more frequently phenoconverted to pDLB.

Survival analysis revealed that the pPD label (Figure 2A) was only moderately associated with phenoconversion (aHR 1.42, 95% confidence interval (CI), 0.87–2.31). Conversely, the pDLB label (Figure 2B) was significantly associated with phenoconversion (aHR 1.84, 95% CI 1.12–3.04), especially when it was combined with the pPD label (Figure 2C, aHR 2.34, 95% CI 1.24–4.41). Interestingly, people without either pPD or pDLB labels (i.e., "truly" clinically isolated RBD) were significantly more likely not to phenoconvert at the last available follow-up (Figure 2C, aHR 0.43, 95% CI 0.23–0.81).

5 | Discussion

This longitudinal multicenter study aimed to describe the baseline and follow-up characteristics of a large group of people diagnosed with iRBD, particularly by exploring the overlap between the nosological label of iRBD with pPD and pDLB labels. We found that the majority of iRBD patients fulfilled at least one of the pPD/pDLB labels, whereas approximately one-third of them did not meet any of them. Interestingly, a non-negligible portion (14.4%) of iRBD patients had both prodromal labels at the same time. Notably, the pPD/pDLB labels currently are for research purposes only, whereas iRBD is a nosological classification approved for clinical practice. These findings highlight the vast heterogeneity of iRBD patients, suggesting that patients may receive different diagnostic labels. Thus, they likely receive different health care approaches and management methods, including the use of different biomarkers to better characterize the disease [19], depending on the personal specific expertise of the consulting neurologist who first encounters the patient.

Most importantly, the use of pPD/pDLB labels has relevant prognostic value. Indeed, iRBD patients with pPD/pDLB labels have an increased risk of phenoconversion in the short term, especially when both criteria are met. This increased risk is expected because a certain number of clinical features are needed to fulfill pPD/pDLB labels. Thus, the presence of a prodromal label indirectly implies the presence of other neurological signs and symptoms. However, our data raise two intriguing issues. First, the specific clinical label (i.e., pPD or pDLB) did not predict the respective outcome (i.e., PD or DLB). This finding highlights the concept that PD and DLB are on the same clinical continuum, as also suggested in the new biological definition of PD and neuronal alpha-synuclein disease [8, 9], and confirms the notion that clinical data alone poorly predict the phenoconversion trajectory [3–5]. Second, iRBD patients fulfilling both the pPD and pDLB criteria had the highest risk of phenoconversion in the short term. This finding is likely due to the presence of a multitude of clinical signs and symptoms in these subgroups of patients, allowing them to meet the criteria of both labels, which suggests the importance of a comprehensive clinical assessment in iRBD that should always include motor, cognitive, autonomic, and olfaction evaluations.

In the sample examined in this study, several features, such as hyposmia, as well as a pPD diagnosis, were less common than in recent multicentric studies [5, 20]. This difference may be

TABLE 2 | Clinical and demographic characteristics of iRBD people, according to their prodromal diagnosis labels.

	None	pPD only	pDLB only	Both pPD and pDLB	*p*
N	86 (30.2%)	142 (49.8%)	16 (5.6%)	41 (14.4%)	
Sex, males	83.7%	83.1%	75%	70.7%	0.260
Education, years	10.8 ± 4.4 [9]	10.0 ± 4.2 [8]	8.8 ± 4.1 [8]	9.5 ± 4.3 [8]	0.316
Age, years	65.8 ± 8.1 [67]	68.7 ± 7.9 [73]	69.9 ± 9.8 [73]	71.0 ± 6.6 [71]	**0.001**
Symptoms duration, months	60.8 ± 58.7 [51]	66.2 ± 53.9 [60]	51.9 ± 41.2 [48]	51.4 ± 50.6 [36]	0.372
MDS-UPDRS-III	2.0 ± 1.5 [2]	3.2 ± 3.3 [2]	2.0 ± 1.6 [2]	2.8 ± 3.6 [2]	**0.017**
MMSE	27.8 ± 2.0 [28]	27.7 ± 2.3 [28]	26.1 ± 2.6 [27]	26.1 ± 2.8 [26]	**< 0.001**
MCI	0%	0%	100%	100%	**< 0.001**
DaT-SPECT					**< 0.001**
Normal	83.9%	47.4%	85.7%	30.8%	
Unilateral putaminal reduced uptake	3.6%	20.7%	0%	28.2%	
Bilateral putaminal reduced uptake	12.5%	25.9%	14.3%	30.8%	
Diffuse reduced uptake	0%	6.0%	0%	10.3%	
Hyposmia	21.7%	59.3%	20.0%	52.5%	**< 0.001**
First medical complaint					**0.017**
Dream-enacting behaviors	86.0%	84.5%	81.2%	80.5%	
Motor symptoms	2.3%	1.4%	0%	0%	
Cognitive symptoms	3.5%	0.7%	12.5%	14.6%	
Other sleep disorders	4.7%	11.3%	6.2%	2.4%	
Other	3.5%	2.1%	0%	2.4%	
Follow-up time, months	41.0 ± 43.8 [28]	42.1 ± 48.0 [27]	34.8 ± 24.8 [29]	36.8 ± 31.9 [28]	0.860
Phenoconverted	23.3%	26.1%	18.8%	53.7%	**0.002**
Phenoconversion diagnosis					0.124
PD	45.0%	73.0%	66.7%	36.4%	
DLB	45.0%	24.3%	33.3%	59.1%	
MSA	10.0%	2.7%	0%	4.5%	

Note: Continuous variables are shown as mean ± standard deviation [median]. Categorical variables are shown as percentage. Significant *p* values are in bold.
Abbreviations: DaT, dopamine transporter; DLB, dementia with Lewy bodies; MCI, mild cognitive impairment; MDS-UPDRS-III, movement disorder society unified Parkinson's disease rating scale motor section; MMSE, mini mental state examination; MSA, multiple system atrophy; PD, Parkinson's disease.

related to the lower phenoconversion rate in our study (approximately 30%) than in published studies (up to 73%), indicating that our sample likely included a greater percentage of subjects in earlier stages.

Notably, approximately 16% of the iRBD patients enrolled in the present study were admitted to a neurology clinic not complaining of dream-enacting behaviors but other neurological symptoms, including motor and cognitive impairment, and were then referred to the sleep lab when suspected RBD emerged during the consultation. Thus, if the neurologist would not have questioned about sleep, RBD may have remained undiagnosed. This finding further highlights the importance of specific sleep medicine training for neurologists [21].

Taken together, these findings suggest that the terms "idiopathic" and "clinically isolated" no longer seem adequate, at least for most people with iRBD. The term "idiopathic" is likely the most outdated because it implies that the underlying cause of the disease is unknown, whereas most, if not all, iRBD cases are due to underlying alpha-synucleinopathy. However, the current term "clinically isolated" is also misleading because it suggests that RBD is the only clinical complaint reported in these patients, whereas most of patients also have mild motor, cognitive, and autonomic signs and symptoms [5]; in our sample, approximately 16% of the subjects sought medical attention not for dream-enacting behaviors, but for other symptoms. Thus, switching from a descriptive lexicon (i.e., clinically isolated RBD) to a biology-driven lexicon should be considered.

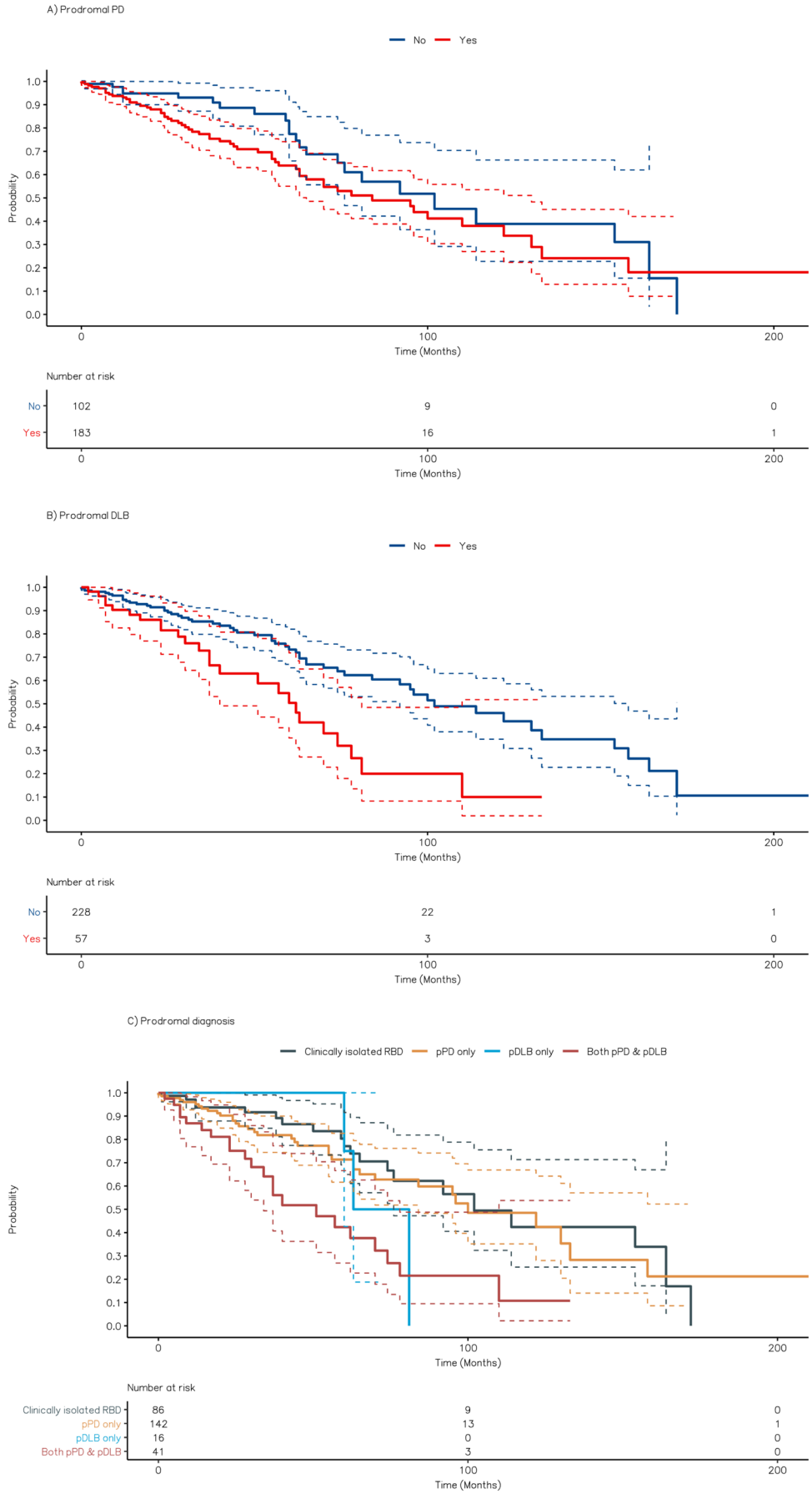

FIGURE 2 | Kaplan–Meier estimation curves of prodromal criteria in iRBD people. (A) Prodromal PD only. (B) Prodromal DLB. (C) Prodromal diagnosis. The dotted lines represent the 95% confidence interval.

This approach has already been applied in the Alzheimer's disease (AD) field, where the prodromal (i.e., predementia) AD stage is known to be characterized by the presence of MCI. In 2011, the National Institute on Aging-Alzheimer's Association (NIA-AA) workgroups on diagnostic guidelines for AD suggested that when a clinical diagnosis of MCI is made, biomarkers should be used to establish the underlying etiology responsible for the clinical deficit [22]. This finding was recognized as extremely important because MCI may be due to several underlying etiologies, including but not limited to AD. Similarly, RBD is a clinical diagnosis but has a multitude of underlying etiologies, including alpha-synucleinopathy, but also narcolepsy and brainstem lesions.

The present study revealed that approximately 30% of the enrolled subjects were affected by RBD due to alpha-synucleinopathy because of the development of overt PD, DLB or MSA at follow-up. However, approximately 70% of the enrolled subjects presented with a multitude of subtle yet detectable signs and symptoms that allowed them to be diagnosed with prodromal PD and/or DLB. This finding is in line with literature data obtained from large multicentric iRBD cohorts showing that in up to 73% of iRBD patients, RBD is due to alpha-synucleinopathy because of the phenoconversion to overt PD, DLB or MSA over time, when an adequately long follow-up is available [3–5, 12, 20]. Notably, more than 95% of iRBD patients have a positive alpha-synuclein biomarker [10, 11]. Overall, these findings further stress that both "idiopathic" and "clinically isolated" terms are likely no longer adequate and possibly even misleading for the majority of people currently labeled as iRBD.

Based on this evidence, we suggest launching an international initiative involving the International RBD Study Group (IRBDSG), international neurological and sleep societies, and relevant stakeholders to define a new lexicon for people with a polysomnography-confirmed diagnosis of RBD, incorporating relevant biomarkers to clearly define the underlying etiologies of the disease. This initiative may allow us to clearly differentiate RBD due to alpha-synucleinopathy from RBD due to other etiologies, such as narcolepsy and brainstem lesions, by identifying the biomarkers that should be used, as well as their manner and timing of use. Moreover, a new lexicon may more explicitly identify people with an underlying neurodegenerative disorder, with relevant implications for the enrollment criteria in trials with disease-modifying drugs, by clearly defining the target population. Indeed, polysomnography-proven RBD due to alpha-synucleinopathy is currently considered the best target for future disease-modifying clinical trials [23].

In conclusion, the results of this study show the large heterogeneity of people suffering from iRBD, highlighting the relevant outcome implications of the presence of clinical and neuroimaging features in this population. As the availability of both pathological (i.e., alpha synuclein) and downstream neurodegeneration (e.g., nigrostriatal damage) biomarkers is increasing, the labels of 'idiopathic' and 'clinically isolated' RBD now seem outdated; thus, we envision an international initiative to define a biomarker-based, biology-driven lexicon to clearly identify the underlying etiologies of RBD. Indeed, the current terminology includes, under a wide umbrella term of idiopathic/clinically isolated RBD, all patients with RBD without overt neurology signs or symptoms (i.e., Parkinsonism or dementia). However, most of these patients (if not all) already have an incipient alpha-synucleinopathy, and they will soon develop overt Parkinsonism or dementia. Moreover, most patients (at least 70% in our sample) are not clinically isolated, but rather exhibit several other signs and symptoms likely related to an incipient alpha-synucleinopathy. Thus, the current terminology should be revised to better reflect the clinical and biological picture of RBD patients. Moreover, it is known that the use of biomarkers improves the ability in identifying RBD patients at high risk of phenoconversion. These biomarkers include clinical assessment (such as motor, cognitive, olfaction, and autonomic assessment), as well as imaging techniques (such as DaT-SPECT, but likely alpha-synuclein assays in the skin or CSF will definitely be useful). Therefore, in our view, the new lexicon should incorporate the use of biomarkers. However, to better detail which biomarkers should be used, and the exact new lexicon is beyond the aim of the present study, which is intended to suggest launching a joint international societies initiative to clearly define a new and shared terminology to better define patients with RBD.

Author Contributions

Dario Arnaldi: conceptualization, methodology, software, data curation, investigation, validation, formal analysis, supervision, funding acquisition, visualization, project administration, resources, writing – original draft. **Pietro Mattioli:** methodology, data curation, writing – review and editing, investigation. **Beatrice Orso:** investigation, data curation, writing – review and editing. **Federico Massa:** data curation, investigation, writing – review and editing. **Matteo Pardini:** data curation, investigation, writing – review and editing, conceptualization. **Silvia Morbelli:** conceptualization, investigation, data curation, writing – review and editing. **Flavio Nobili:** conceptualization, data curation, writing – review and editing, investigation. **Michela Figorilli:** investigation, data curation, writing – review and editing. **Elisa Casaglia:** investigation, writing – review and editing, data curation. **Martina Mulas:** investigation, data curation, writing – review and editing. **Michele Terzaghi:** conceptualization, investigation, writing – review and editing, data curation. **Elena Capriglia:** investigation, writing – review and editing, data curation. **Gaetano Malomo:** investigation, writing – review and editing, data curation. **Michela Solbiati:** investigation, writing – review and editing, data curation. **Elena Antelmi:** conceptualization, investigation, writing – review and editing, data curation. **Fabio Pizza:** investigation, writing – review and editing, data curation. **Francesco Biscarini:** investigation, writing – review and editing, data curation. **Monica Puligheddu:** conceptualization, investigation, funding acquisition, writing – review and editing, data curation. **Giuseppe Plazzi:** conceptualization, investigation, writing – review and editing, data curation.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author (D.A.) upon reasonable request.

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