

## ORIGINAL ARTICLE

# Clinical and dopaminergic imaging characteristics of the FARPRESTO cohort of trial-ready idiopathic rapid eye movement sleep behavior patients

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## Abstract

**Introduction:** Idiopathic/isolated rapid eye movement (REM) sleep behavior disorder (iRBD) is considered the prodromal stage of alpha-synucleinopathies. Thus, iRBD patients are the ideal target for disease-modifying therapy. The risk FAcToRs PRedictive of phe-noconversion in iRBD Italian STudy (FARPRESTO) is an ongoing Italian database aimed

Dario Arnaldi and Pietro Mattioli contributed equally to this work.

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at identifying risk factors of phenoconversion, and eventually to ease clinical trial enrollment of well-characterized subjects.

**Methods:** Polysomnography-confirmed iRBD patients were retrospectively and prospectively enrolled. Baseline harmonized clinical and nigrostriatal functioning data were collected at baseline. Nigrostriatal functioning was evaluated by dopamine transporter-single-photon emission computed tomography (DaT-SPECT) and categorized with visual semi-quantification. Longitudinal data were evaluated to assess phenoconversion. Cox regressions were applied to calculate hazard ratios.

**Results:** 365 patients were enrolled, and 289 patients with follow-up (age  $67.7 \pm 7.3$  years, 237 males, mean follow-up  $40 \pm 37$  months) were included in this study. At follow-up, 97 iRBD patients (33.6%) phenoconverted to an overt synucleinopathy. Older age, motor and cognitive impairment, constipation, urinary and sexual dysfunction, depression, and visual semi-quantification of nigrostriatal functioning predicted phenoconversion. The remaining 268 patients are in follow-up within the FARPRESTO project.

**Conclusions:** Clinical data (older age, motor and cognitive impairment, constipation, urinary and sexual dysfunction, depression) predicted phenoconversion in this multicenter, longitudinal, observational study. A standardized visual approach for semi-quantification of DaT-SPECT is proposed as a practical risk factor for phenoconversion in iRBD patients. Of note, non-converted and newly diagnosed iRBD patients, who represent a trial-ready cohort for upcoming disease-modification trials, are currently being enrolled and followed in the FARPRESTO study. New data are expected to allow better risk characterization.

### KEYWORDS

dementia, multiple system atrophy, Parkinson's disease, REM sleep behavior disorder, synucleinopathy

## INTRODUCTION

Rapid eye movement (REM) sleep behavior disorder (RBD) is a REM sleep parasomnia characterized by the loss of the physiological REM sleep atonia and the enactment of dreams [1]. When it is not associated with overt neurological symptoms the descriptor 'idiopathic/isolated' is added (iRBD). However, iRBD precedes the diagnosis of the overt stage of alpha-synucleinopathies (Parkinson's disease [PD], dementia with Lewy bodies [DLB], and multiple systemic atrophy [MSA]) in most middle-aged and older adult cases if patients have a sufficiently long follow-up [2]. Moreover, most iRBD patients have biological evidence of alpha-synucleinopathy in skin biopsy [3, 4] and in cerebrospinal fluid [5, 6], indicating that iRBD patients are in a prodromal stage of alpha-synucleinopathy. However, iRBD patients are highly heterogeneous and the time from the onset of symptoms to the phenoconversion is variable. Therefore, the prediction of the clinical outcome in iRBD patients is of utmost importance.

In 2019, a large multicentric study was performed to compare the risk factors for phenoconversion in iRBD patients from 24 centers worldwide within the International RBD Study Group (IRBDSG) [7]. The authors found that abnormal quantitative motor testing (hazard ratio [HR]=3.16), objective motor examination (HR=3.03), olfactory deficit (HR=2.62), mild cognitive impairment (MCI) (HR=3.03),

erectile dysfunction (HR=2.13), motor symptoms (HR=2.11), abnormal dopamine transporter-single-photon emission computed tomography (DaT-SPECT) (HR=1.98), color vision abnormalities (HR=1.69), constipation (HR=1.67), REM atonia loss (HR=1.54), and age (HR=1.54) significantly increased the risk of phenoconversion at follow-up. Afterwards, another multicenter study within the IRBDSG showed that the DaT-SPECT is among the best predictors of phenoconversion (HR=4.35) if properly quantified and not only using a dichotomic 'normal/abnormal' classification [8].

Recently the North American Prodromal Synucleinopathy (NAPS) Consortium for RBD published the results of a cross-sectional study on 361 iRBD patients from nine sites in North America. The study reflects the need for better phenotyping iRBD patients in the view of possible disease-modifying clinical trials [9].

The risk FACToRs PRedictive of phenoconversion in idiopathic REM sleep behavior disorder Italian Study (FARPRESTO) [10] is a multicentric, Italian, longitudinal, retrospective and prospective project, promoted by the Italian Association of Sleep Medicine (AIMS; [www.sonnomed.it](http://www.sonnomed.it)) and endorsed by the Italian association of patients with RBD ([www.associazionerbd.it](http://www.associazionerbd.it)), currently involving 14 Italian sleep centers. The FARPRESTO project has several aims, including the investigation of biomarkers able to predict phenoconversion in iRBD. Moreover, being a living database of iRBD

patients, enrolled with standardized and harmonized procedures, the FARPRESTO study is de facto building a trial-ready cohort of patients for upcoming disease-modifying clinical trials.

The primary aim of the present study was to investigate the risk and predictors of parkinsonism and dementia in the FARPRESTO cohort, comparing the results with the recent international IRBDSG study [7]. As a secondary aim, we explored whether a standardized semi-quantitative visual scoring of DaT-SPECT may be a good predictor of early phenoconversion.

## PATIENTS AND METHODS

To achieve the aim of the present study, we used iRBD patients that were enrolled in the FARPRESTO study in March 2022. Enrolled iRBD patients met the inclusion/exclusion criteria of the FARPRESTO study [10]. In brief, the diagnosis of RBD was performed according to current international criteria including confirmation by means of an overnight polysomnographic recording [11]. At baseline, the presence of dementia was excluded by exploring the activities of daily living and instrumental activity of daily living, and the criteria for the diagnosis of PD and MSA were not satisfied [12–14]. Other psychiatric or neurological conditions were ruled out. Brain structural alterations were ruled out by performing brain magnetic resonance imaging (MRI) or computed tomography (CT).

At baseline, the study protocol foresees a sociodemographic assessment and a minimum set of clinical data. Mandatory data included a patient's demographic features, current medical history, current therapy, the use of alcohol and recreational substances, family history, physical activity, and dream content. Moreover, a minimum set of clinical data, including date of RBD diagnosis, Unified Parkinson's Disease Rating Scale-Part III (UPDRS-III) or Movement Disorders Society-Unified Parkinson's Disease Rating Scale-Part III (MDS-UPDRS-III); Mini-Mental State Examination (MMSE), or Montreal Cognitive Assessment (MoCA); neuroimaging evaluation (brain MRI or brain CT) were provided. Details are provided in the study protocol. Each center had the possibility to provide further biomarkers following the three-level assessment described in the study protocol [10]. In the present study, only MDS-UPDRS III and MMSE scores were used for the analysis.

Of note, a subset of patients also underwent advanced biomarkers, including brain DaT-SPECT with [<sup>123</sup>I]-FP-CIT (123-radiolabeled 2β-carbomethoxy-3β-(4-iodophenyl)-N-(3-fluoropropyl)-nortropane) to assess nigrostriatal pathway functioning, acquired according to the European Association of Nuclear Medicine's (EANM) guidelines [15]. Following the FARPRESTO protocol [10], the DaT-SPECT scans were visually categorized, by an experienced molecular imaging specialist, as follows: (i) normal, (ii) unilateral putaminal alteration, (iii) bilateral putaminal alteration, (iv) diffuse alteration, and (v) atypical pattern, if none of the aforementioned possibilities were met.

All participating centers were asked to prospectively evaluate the patients at least every 12 months to assess for phenoconversion to DLB, PD, or MSA, according to international criteria [12–14].

Only patients with a follow-up of at least 6 months were included in the present analysis. Patients who did not phenoconvert were referred to as non-converter patients, whereas patients who did phenoconvert were converter patients. Depending on which overt alpha-synucleinopathy the patient converted to, they were further classified as DLB-converters, PD-converters, and MSA-converters.

All procedures performed in studies involving human participants were in accordance with the ethical standards of institutional and/or national research committees and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Informed consent was obtained from all individual participants included in the study.

## Statistical analysis

The baseline demographic, clinical, and DaT-SPECT, categorized by an experienced molecular imaging specialist in each center, were compared between converter and non-converter patients and between DLB-converters and PD-converters (because of the lower number, MSA-converters were excluded from this analysis) by applying a receiver operating characteristic (ROC) analysis. The Youden index method was used to identify the optimal threshold to distinguish the two groups [16].

To determine the power in predicting phenoconversion, Kaplan–Meier survival analysis was first computed, then the hazard ratio (HR) was calculated with a Cox regression analysis for each variable. The survival time was considered as the time (in months) from the baseline visit and the last follow-up visit for non-converter patients and to the diagnosis of the overt alpha-synucleinopathy for converter patients. Age, sex, and center were used as covariates in the analysis.

Statistical analyses were performed using Stata software (Stata Statistical Software: Release 13, 2013; StataCorp LP, College Station, TX, USA).

## RESULTS

In March 2022, 365 iRBD patients were enrolled in the FARPRESTO study from nine Italian centers: Bologna (two centers), Cagliari, Genoa, Milano, Pavia, Pisa, Rome Gemelli, and Rome Tor Vergata. Among these, 289 patients (age  $67.7 \pm 7.3$  years, 237 males, 82% males, mean follow-up  $40 \pm 37$  months) had at least 6 months of follow-up and were included in the analysis. At follow-up, 97 iRBD patients (33.6%) phenoconverted (mean phenoconversion time  $43.8 \pm 37.8$  months), and in particular 56 patients converted to PD (57.7%), 36 to DLB (37.1%), and 5 to MSA (5.2%).

Demographic, clinical, and DaT-SPECT data comparisons between converter and non-converter patients are shown in Table 1. The significant clinical risk factors for phenoconversion were older age (HR 1.07), higher MDS-UPDRS-III score (HR 2.26), presence of MCI (HR 1.97), constipation (HR 2.46), urinary dysfunction (HR 3.39), sexual dysfunction (HR 3.56), and depression (HR 2.20).

A total of 136 patients underwent DaT-SPECT acquisition. The visual semi-quantification of DaT-SPECT data also significantly predicted phenoconversion. Interestingly, the DaT-SPECT pattern 1 (unilateral putaminal alteration) did not achieve statistical significance, while the HR increased along with the severity of the DaT-SPECT alteration.

No significant results were found when comparing DLB-converters and PD-converters. Kaplan–Meier survival curves for each variable are shown in Figure 1 (clinical biomarkers) and Figure 2 (DaT-SPECT).

## DISCUSSION

Here, we present the preliminary data of the FARPRESTO study [10], an Italian multicentric project aimed at collecting and analyzing longitudinal data from iRBD patients. This is an observational study with a cohort of incident (prospective recruitment) and prevalent (retrospective recruitment) iRBD patients, promoted by the Italian Association of Sleep Medicine (AIMS; [www.sonnomed.it](http://www.sonnomed.it)) and endorsed by the Italian Association of Patients with RBD ([www.associazionerbd.it](http://www.associazionerbd.it)). The project is currently ongoing, and

**TABLE 1** Clinical, demographic, and [ $^{123}$ ]I-FP-CIT-SPECT biomarkers.

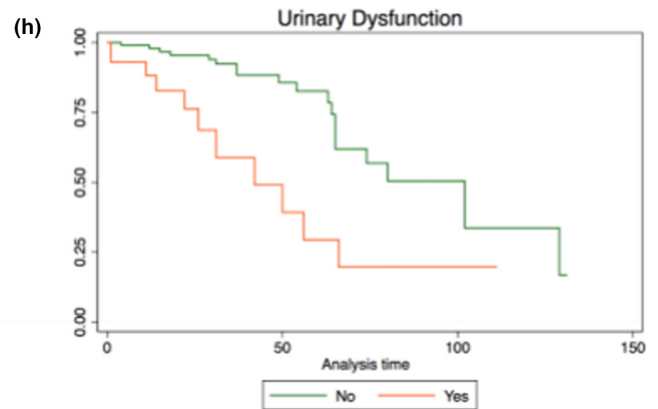
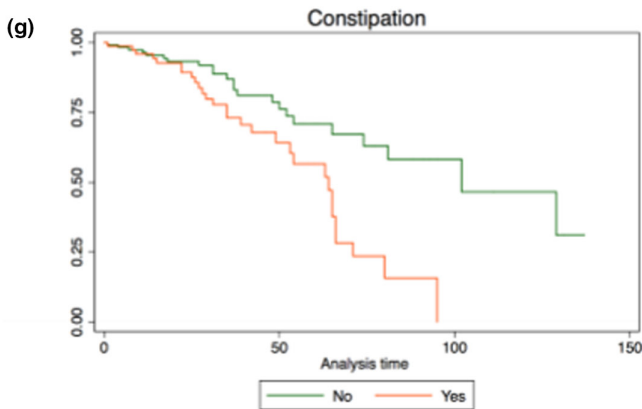
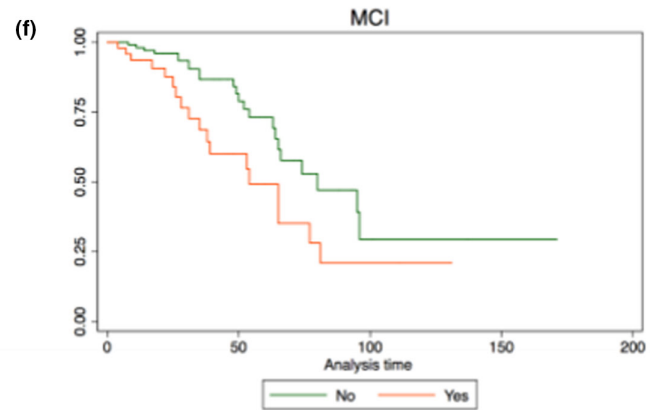
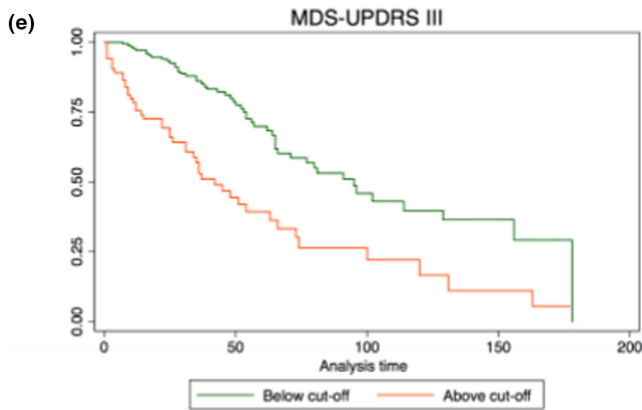
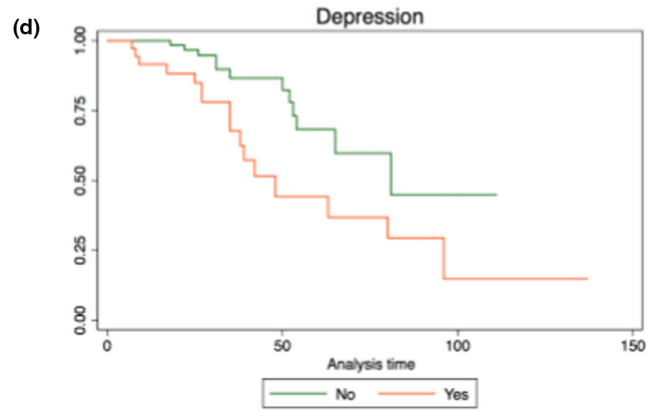
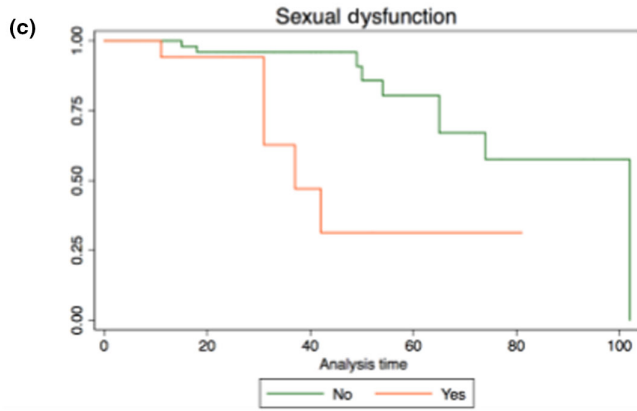
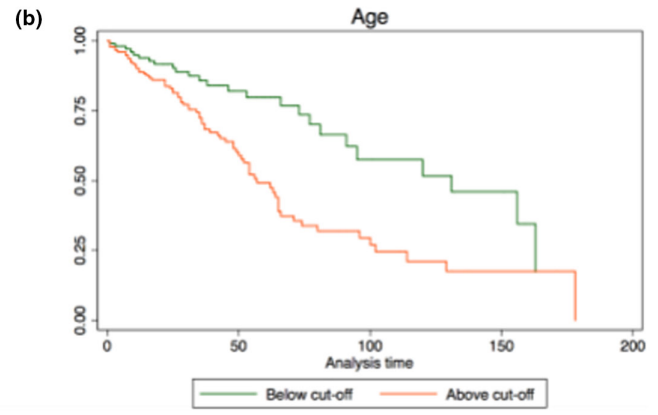
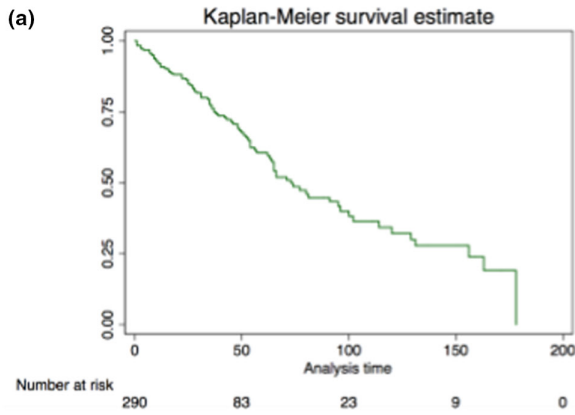
Variable	Converters (n = 97)	Non-converters (n = 192)	Age-, sex-, and center-adjusted HR (95% CI)
Age, years	68.79 ± 6.5 (n = 97)	67.21 ± 7.6 (n = 192)	1.07 (1.03–1.10)
Sex, males	81.6% (n = 97)	82.3% (n = 192)	1.17 (0.69–2.00)
Education, years	10.41 ± 4.0 (n = 66)	9.96 ± 4.2 (n = 144)	1.02 (0.96–1.09)
RBD symptom duration, months	60.00 ± 64.9 (n = 58)	66.50 ± 56.5 (n = 164)	1.01 (0.58–1.77)
MDS-UPDRS-III	3.74 ± 4.4 (n = 97)	1.70 ± 2.5 (n = 192)	2.26 (1.48–3.46)
MMSE	27.06 ± 2.8 (n = 97)	28.01 ± 2.2 (n = 192)	1.14 (0.74–1.75)
MCI	43.9% (n = 41)	26.98% (n = 126)	1.97 (1.02–3.79)
Regular smoking	15.7% (n = 70)	30.4% (n = 138)	0.73 (0.38–1.42)
Regular alcohol use <sup>a</sup>	36.1% (n = 61)	45.1% (n = 122)	0.75 (0.44–1.29)
Toxic substances exposure	6.3% (n = 48)	4.7% (n = 107)	0.65 (0.20–2.19)
Family history of dementia/parkinsonism	25.0% (n = 72)	15.97% (n = 144)	1.02 (0.60–1.76)
Regular physical exercise	8.3% (n = 24)	29.4% (n = 68)	0.39 (0.09–1.71)
RBD-related lesions	57.4% (n = 68)	66.7% (n = 138)	0.69 (0.41–1.14)
Hyposmia	40.8% (n = 49)	48.3% (n = 145)	1.40 (0.76–2.59)
Constipation	55.8% (n = 52)	33.8% (n = 151)	2.46 (1.38–4.40)
Urinary dysfunction	36.7% (n = 30)	16.5% (n = 109)	3.39 (1.55–7.40)
Sexual dysfunction	35.7% (n = 14)	19.7% (n = 71)	3.56 (1.02–12.48)
Orthostatic hypotension	19.6% (n = 51)	17.6% (n = 148)	1.63 (0.78–3.42)
Depression	57.1% (n = 28)	23.4% (n = 94)	2.20 (1.01–4.82)
Visual hallucinations	3.7% (n = 27)	1% (n = 96)	7.21 (0.76–68.39)
[ $^{123}$ ]I-FP-CIT-SPECT, abnormal	63.4% (n = 41)	41.1% (n = 95)	3.49 (1.74–7.00)
Unilateral putaminal alteration	12.2% (n = 5)	23.2% (n = 22)	1.85 (0.65–5.32)
Bilateral putaminal alteration	39.0% (n = 16)	14.7% (n = 14)	3.72 (1.72–8.06)
Diffuse alteration	12.2% (n = 5)	3.2% (n = 3)	11.66 (3.85–35.28)

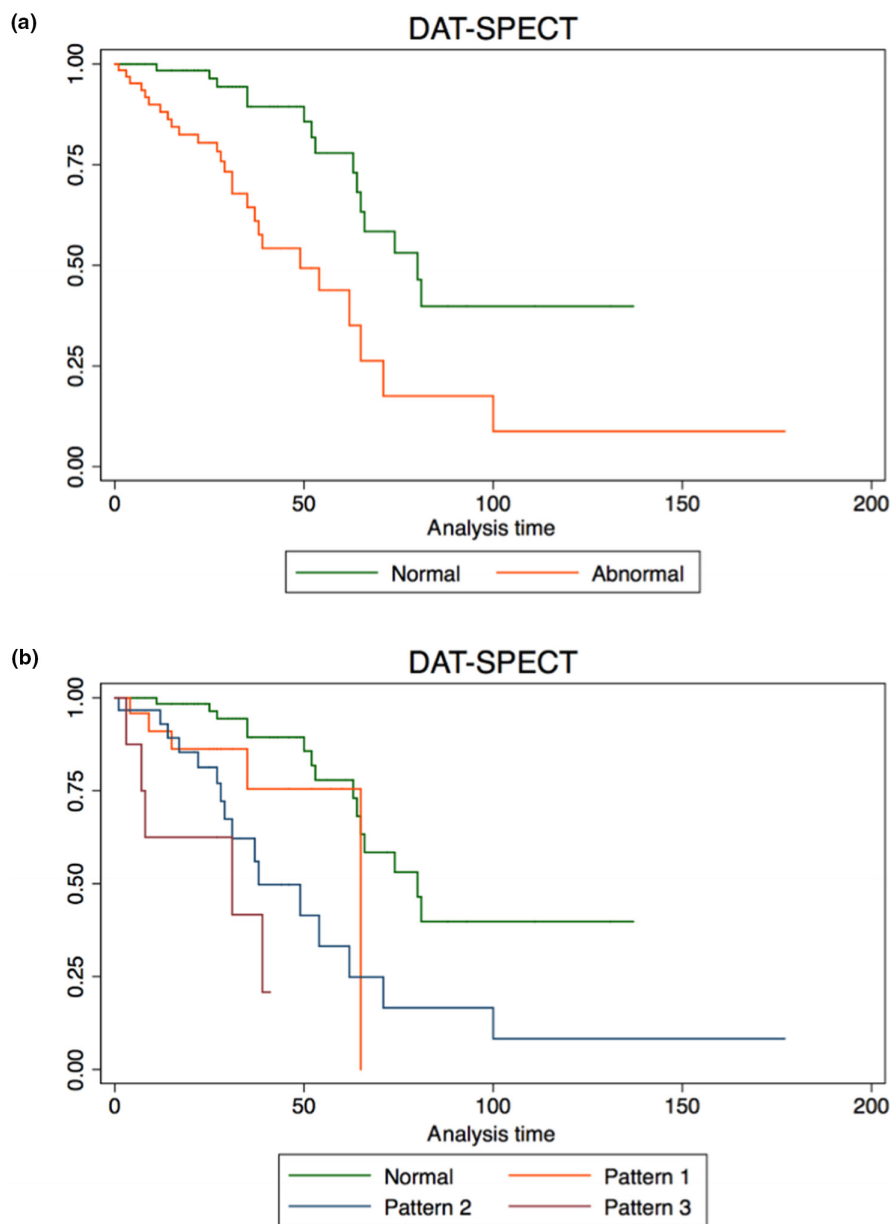
Note: Data are reported in terms of mean ± standard deviation (total number). In the final column, hazard ratios and confidence intervals are reported. Statistically significant values are in bold type.

Abbreviations: [ $^{123}$ ]I-FP-CIT-SPECT, 123-radiolabeled 2β-carbomethoxy-3β-(4-iodophenyl)-N-(3-fluoropropyl)-nortropine-single positron emission computed tomography; CI, confidence interval; HR, hazard ratio; MCI, mild cognitive impairment; MDS-UPDRS-III, Movement Disorder Society-Unified Parkinson Disease Rating Scale-Part III; MMSE, Mini-Mental State Examination; PSQI, Pittsburgh Sleep Quality Index; RBD, rapid eye movement (REM) sleep behavior disorder.

<sup>a</sup>At least one drink per day.

**FIGURE 1** Kaplan–Meier analysis: epidemiological and clinical variables. The survival time is expressed in months (a) Kaplan–Meier survival estimate, (b) age, (c) sexual dysfunction, (d) depression, (e) Movement Disorder Society-Unified Parkinson Disease Rating Scale-Part III (MDS-UPDRS-III), (f) mild cognitive impairment (MCI), (g) constipation, and (h) urinary dysfunction. [Colour figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]





**FIGURE 2** Kaplan–Meier analysis: [ $^{123}\text{I}$ ]-FP-CIT-SPECT (123-radiolabeled 2 $\beta$ -carbomethoxy-3 $\beta$ -(4-iodophenyl)-N-(3-fluoropropyl)-nortropane-single positron emission computed tomography). (a) The dichotomic normal/abnormal classification is shown. (b) When a semi-quantitative categorization is used, a survival gradient from normal to pattern 3 can be noticed. Pattern 1 is more similar to normal, pattern 2 is more similar to pattern 3. [Colour figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

at March 2022, 365 iRBD patients were enrolled, of whom 289 patients already had at least 6 months of follow-up. Among the enrolled patients, 97 iRBD patients (33.6%) developed an overt synucleinopathy over time, meaning that the remaining 268 are still free from overt alpha-synucleinopathy, and are being followed within the FARPRESTO project. Those patients, together with new patients that will be further enrolled in the study, constitute a well-characterized trial-ready cohort for upcoming disease-modifying trials. Indeed, according to the FARPRESTO protocol [10], all patients will be collected with harmonized procedures, and followed over time with standardized assessment. A similar initiative is ongoing in North America, namely the North American Prodromal Synucleinopathy (NAPS) Consortium (<https://www.naps-rbd.org>). The NAPS Consortium had enrolled, as of April 2021, 361 patients.

Several putative disease-modifying therapies targeting alpha-synuclein are now being developed [17], but the clinical trials using such therapies in PD are failing in achieving both clinical and imaging efficacy endpoints [18, 19]. Besides some methodological issues, one reason is the possible lack of efficacy while using disease-modifying treatments in patients with already overt neurodegenerative disease. Testing such therapies on prodromal stages of alpha-synucleinopathies, namely iRBD patients, may increase the likelihood of success. A recent proof-of-concept study suggesting that disease-modifying trials in iRBD are feasible [20] claims to have collected trial-ready cohorts of iRBD patients in which disease-modifying trials could be easily developed and tested.

The preliminary results presented here largely confirm what has been described in previous IRBDSG studies [7, 8]. In particular, older age, motor symptoms, presence of MCI, constipation, sexual

dysfunction, and an abnormal DaT-SPECT significantly increased the risk of phenoconversion at follow-up. Conversely, in the present study, other biomarkers such as hyposmia did not yield significant prediction abilities, possibly because of the different methodology.

A recent review by the IRBDSG summarized the available data in the literature about the biomarkers of phenoconversion in iRBD [21], and the results of the present study largely overlap with the risk factors summarized in the IRBDSG's review. However, it must be highlighted that most of the data in the literature relates to the investigation of individual biomarkers and not clusters of biomarkers. In future studies it would be interesting to investigate the most promising biomarkers by using multivariate approaches.

A new and intriguing result is the high predictive power of the visual semi-quantification of DaT-SPECT data. In fact, in the previous IRBDSG study, only a dichotomic normal/abnormal classification of the nigrostriatal pathway was used, finding significant results, but with an unexpected relatively low HR. [7] Indeed, a subsequent IRBDG study demonstrated that if DaT-SPECT data are centrally analysed by using a semi-quantitative software, nigrostriatal dopaminergic impairment is among the best risk factors for phenoconversion in iRBD patients [8]. However, performing such analysis may increase the complexity of an eventual disease-modifying trials. Here, we categorized the scans of the patients with a standardized semi-quantitative visual analysis. Using this approach, we have successfully increased the prediction power of DaT-SPECT (HR=3.49) compared with the dichotomous assessment of the previous IRBDSG 2019 study (HR=1.98) [7], but this is still lower compared with the IRBDSG 2021 study that used software-based semi-quantification (HR=4.35) [8]. Therefore, if confirmed in larger, multicentric studies, the visual semi-quantification of DaT-SPECT may be considered as a possible biomarker of phenoconversion in iRBD, to be used for patient selection in disease-modifying clinical trials.

We have also to acknowledge some limitations in the present study. Not all patients had all biomarkers, and in particular color vision abnormalities and REM sleep atonia loss were not assessed in the present study. Nevertheless, these data were collected in a large number of the participants and they will be investigated in further studies of the FARPRESTO project. It has to be highlighted that even if about half of the enrolled patients in the FARPRESTO study were also included in the previous IRBDSG study [7], the follow-up time for these patients is longer in the present study, and so the two datasets are substantially different. Moreover, the absence of hyposmia as a predictor of phenoconversion is an unexpected finding and deviates substantially from previously published results. A bias could reside in the different methods of the studies. In fact, in the IRBDSG study the assessment of hyposmia was performed by means of a structured assessment [7] (12- or 40-item University of Pennsylvania Smell Identification Test [22] or Sniffin Sticks [23]), whereas in our study the presence of hyposmia was rated during the patients' anamnestic interview and was not assessed using validated tests, thus possibly reducing the sensitivity of the assessment. This result suggests the importance of performing a structured assessment of hyposmia to enhance the sensitivity of the evaluation.

In conclusion, with the FARPRESTO project providing a 'trial-ready' cohort for upcoming clinical trials in the prodromal stage of alpha-synucleinopathies, we confirmed some results from the previous IRBDSG's studies, pinpointing that motor, cognitive, and autonomic symptoms are reliable clinical predictors of phenoconversion in an independent sample of iRBD patients. Moreover, we suggest that a standardized visual semi-quantification of DaT-SPECT data may also be used as a stratification tool in disease-modifying trials. Finally, the FARPRESTO project provides a trial-ready cohort for upcoming clinical trials in the prodromal stage of alpha-synucleinopathies.

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## CONFLICT OF INTEREST STATEMENT

Dario Arnaldi: received fees from Fidia, Jazz, and Lundbeck for lectures, consultation, and board participation. Silvia Morbelli: received speaker honoraria from GE Healthcare. Elena Antelmi: received fees from Polifarma for board participation. Federica Provini: received fees from Pfizer, Italfarmaco, and Idorsia for lectures. Claudio Liguori, Mariana Fernandes, Fabio Placidi: reported no disclosures related to this work. The other authors report no competing interests.

## DATA AVAILABILITY STATEMENT

Data used in this study can be obtained upon reasonable request to the corresponding author.

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## REFERENCES

1. Arnulf I. REM sleep behavior disorder: motor manifestations and pathophysiology. *Mov Disord*. 2012;27(6):677-689.
2. Galbiati A, Verga L, Giora E, Zucconi M, Ferini-Strambi L. The risk of neurodegeneration in REM sleep behavior disorder: a systematic review and meta-analysis of longitudinal studies. *Sleep Med Rev*. 2019;43:37-46. doi:10.1016/J.SMRV.2018.09.008
3. Antelmi E, Pizza F, Donadio V, et al. Biomarkers for REM sleep behavior disorder in idiopathic and narcoleptic patients. *Ann Clin Transl Neurol*. 2019;6(9):1872-1876. doi:10.1002/acn3.50833

4. Doppler K, Antelmi E, Kuzkina A, et al. Consistent skin  $\alpha$ -synuclein positivity in REM sleep behavior disorder – a two center two-to-four-year follow-up study. *Parkinsonism Relat Disord*. 2021;86:108-113. doi:10.1016/J.PARKRELDIS.2021.04.007
5. Iranzo A, Fairfoul G, Ayudhaya ACN, et al. Detection of  $\alpha$ -synuclein in CSF by RT-QuIC in patients with isolated rapid-eye-movement sleep behaviour disorder: a longitudinal observational study. *Lancet Neurol*. 2021;20(3):203-212. doi:10.1016/S1474-4422(20)30449-X
6. Poggiolini I, Gupta V, Lawton M, et al. Diagnostic value of cerebrospinal fluid alpha-synuclein seed quantification in synucleinopathies. *Brain*. 2022;145(2):584-595. doi:10.1093/BRAIN/AWAB431
7. Postuma RB, Iranzo A, Hu M, et al. Risk and predictors of dementia and parkinsonism in idiopathic REM sleep behaviour disorder: a multicentre study. *Brain*. 2019;142(3):744-759. doi:10.1016/j.smrv.2018.09.008
8. Arnaldi D, Chincarini A, Hu MT, et al. Dopaminergic imaging and clinical predictors for phenoconversion of REM sleep behaviour disorder. *Brain*. 2021;144(1):278-287. doi:10.1093/BRAIN/AWAA365
9. Elliott JE, Lim MM, Keil AT, et al. Baseline characteristics of the North American Prodromal Synucleinopathy cohort. *Ann Clin Transl Neurol*. 2023;10:520-535. doi:10.1002/acn3.51738
10. Puligheddu M, Figorilli M, Antelmi E, et al. Predictive risk factors of phenoconversion in idiopathic REM sleep behavior disorder: the Italian study "FARPRESTO.". *Neurol Sci*. 2022;1:1-10. doi:10.1007/S10072-022-06374-4/TABLES/3
11. American Academy of Sleep Medicine (AASM). *International Classification of Sleep Disorders – Third Edition (ICSD-3)*. American Academy of Sleep Medicine; 2014.
12. McKeith IG, Boeve BF, Dickson DW, et al. Diagnosis and management of dementia with Lewy bodies. *Neurology*. 2017;89(1):88-100.
13. Postuma RB, Berg D, Stern M, et al. MDS clinical diagnostic criteria for Parkinson's disease. *Mov Disord*. 2015;30(12):1591-1601. doi:10.1002/mds.26424
14. Gilman S, Wenning GK, Low PA, et al. Second consensus statement on the diagnosis of multiple system atrophy. *Neurology*. 2008;71(9):670-676. doi:10.1212/01.wnl.0000324625.00404.15
15. Morbelli S, Esposito G, Arbizu J, et al. EANM practice guideline/SNMMI procedure standard for dopaminergic imaging in parkinsonian syndromes 1.0. *Eur J Nucl Med Mol Imaging*. 2020;47(8):1885-1912. doi:10.1007/s00259-020-04817-8
16. Fluss R, Faraggi D, Reiser B. Estimation of the Youden index and its associated cutoff point. *Biometrical J Math Methods Biosci*. 2005;47(4):458-472.
17. Lang AE, Espay AJ. Disease modification in Parkinson's disease: current approaches, challenges, and future considerations. *Mov Disord*. 2018;33(5):660-677. doi:10.1002/MDS.27360
18. Pagano G, Taylor KI, Anzures-Cabrera J, et al. Trial of prasinumab in early-stage Parkinson's disease. *N Engl J Med*. 2022;387(5):421-432. doi:10.1056/NEJMOA2202867/SUPPL\_FILE/NEJMOA2202867\_DATA-SHARING.PDF
19. Lang AE, Siderowf AD, Macklin EA, et al. Trial of cinpanemab in early Parkinson's disease. *N Engl J Med*. 2022;387(5):408-420. doi:10.1056/NEJMOA2203395/SUPPL\_FILE/NEJMOA2203395\_DATA-SHARING.PDF
20. Arnaldi D, Famà F, Girtler N, et al. Rapid eye movement sleep behavior disorder: a proof-of-concept neuroprotection study for prodromal synucleinopathies. *Eur J Neurol*. 2021;28(4):1210-1217. doi:10.1111/ENE.14664
21. Miglis MG, Adler CH, Antelmi E, et al. Biomarkers of conversion to  $\alpha$ -synucleinopathy in isolated rapid-eye-movement sleep behaviour disorder. *Lancet Neurol*. 2021;20(8):671-684. doi:10.1016/S1474-4422(21)00176-9
22. Doty RL, Shaman P, Dann M. Development of the University of Pennsylvania Smell Identification Test: a standardized microencapsulated test of olfactory function. *Physiol Behav*. 1984;32(3):489-502. doi:10.1016/0031-9384(84)90269-5
23. Mahlknecht P, Iranzo A, Högl B, et al. Olfactory dysfunction predicts early transition to a Lewy body disease in idiopathic RBD. *Neurology*. 2015;84(7):654-658. doi:10.1212/WNL.0000000000001265

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