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Research Article

Nonmotor Symptoms Reduce Quality of Life in Parkinson's Disease Depending on Disease Stage and Age at Onset

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In this observational study, which presents a secondary analysis related to a previously published work from our group, we aimed to examine the impact of nonmotor symptom (NMS) burden on HR-QoL in 154 outpatients with Parkinson's disease (PD), ranging from mild to moderate-advanced disease stages, with a specific focus on motor disease progression and age at onset (AAO). To this purpose, NMS burden was measured using the NMS scale (NMSS), overall HR-QoL using the Parkinson's Disease Questionnaire-39 (PDQ-39), and sleep disturbances using the Parkinson's Disease Sleep Scale-2nd version (PDSS-2). The scores of the three scales were correlated with motor impairment and the amount of dopaminergic therapy. Furthermore, NMSS, PDQ-39, and PDSS-2 scores were compared between early onset PD (EOPD, AAO ≤ 50) and late-onset PD (LOPD, AAO > 50), as well as between "poor sleepers" and "good sleepers" based on the validated PDSS-2 cutoff of 18/60. We found that total NMSS, PDSS-2, and PDQ-39 scores significantly increased with advancing disease stage. EOPD patients had lower NMSS and PDSS-2 global scores compared to LOPD patients, despite the latter having longer disease duration and similar PDQ-39 scores. The NMSS global score correlated with each single domain of the PDQ-39, with the strongest associations observed in the "mobility," "activity of daily living," and "cognition" domains. Over one-third of patients were classified as "poor sleepers" (PDSS-2 ≥ 18) and exhibited higher NMSS and PDQ-39 total scores compared to "good sleepers." In conclusion, this study enlightens the increasing impact of NMS and sleep disturbances on patients' HR-QoL with disease progression and across different AAO, underscoring the need to address such modifiable factors to alleviate the burden of the disease.

Keywords: early onset Parkinson's disease; nonmotor symptoms; Parkinson's disease; quality of life; sleep problems

1. Introduction

Parkinson's disease (PD) is a disabling neurodegenerative disorder characterized by the primary loss of dopaminergic nigral cells and a widespread accumulation of α-synuclein-containing Lewy bodies [1].

In addition to the cardinal motor symptoms, namely, tremor, rigidity, and bradykinesia, PD is burdened by a wide

range of nonmotor symptoms (NMSs) and signs, which often precede the motor manifestations and significantly impact patients' daily functioning and overall health-related quality of life (HR-QoL).

PD is a highly heterogeneous disorder, with different clinical presentations reflecting distinct trajectories of neurodegeneration, which progressively intensify as the disease advances [1], as well as the accompanying immune responses, which shape both motor and nonmotor manifestations [2, 3].

Age at onset (AAO) is a well-known determinant of the clinical presentation of PD. Early onset PD (EOPD), defined by an AAO below 50 years, is generally associated with a lower burden of nonmotor manifestations compared to classical late-onset PD (LOPD). Nevertheless, HR-QoL is often more severely affected in EOPD patients, indicating that other factors may play a role [4].

Over the past two decades, numerous rating scales and questionnaires addressing motor and nonmotor manifestations, as well as tools for measuring HR-QoL, have been developed [5], helping clinicians identify some of the most disabling PD-related features and stratify patients based on their clinical phenotype [6].

Nevertheless, nonmotor features of the disease are often underestimated and not adequately treated, and their relationship with HR-QoL remains poorly investigated, especially with regard to how it varies along disease progression and across different AAO.

Therefore, in this study, a secondary analysis of previously published materials [7, 8], the primary objective was to investigate the impact of the NMS burden on HR-QoL, as evaluated through the validated clinical instruments, NMS Scale (NMSS) [9] and PD Questionnaire-39 (PDQ-39) [10], in a large cohort of PD patients previously investigated for sleep disturbances [7, 8], specifically focusing on the impact of nonmotor manifestations across disease progression.

As a secondary aim, we evaluated differences in NMS and their impact on HR-QoL in relation to AAO and severity of sleep disturbances, comparing clinical scale scores between EOPD ($AAO \leq 50$) and LOPD ($AAO > 50$) and between "good sleepers" and "poor sleepers" defined according to the validated cutoff of 18/60 on the Parkinson's Disease Sleep Scale-2nd version (PDSS-2) [11].

Finally, we examined the relationships between NMS and HR-QoL in the entire cohort and within the identified subgroups.

2. Materials and Methods

2.1. Study Population and Study Design. This manuscript builds upon previously published study data, exploring complementary aspects of the dataset previously generated [7]. The objectives and design of the original single-center, observational study, as well as the inclusion and exclusion criteria, were reported in detail elsewhere [7]. Briefly, the study population consisted of 154 PD outpatients consecutively assessed at the PD Unit of the University Hospital of Rome Tor Vergata (Rome, Italy) between January 2019 and July 2019.

2.2. Inclusion and Exclusion Criteria. The main inclusion criterion was the diagnosis of idiopathic PD made by a movement disorder specialist according to the UK Parkinson's Disease Society Brain Bank criteria (MP, TS, RC, and AS) [12]. Exclusion criteria included atypical or secondary parkinsonism, PD dementia, other neurological and medical conditions affecting sleep, shift work or other circumstances possibly interfering with a regular sleep–wake cycle, and unavailability to complete the self-administered clinical scales.

2.3. Assessments. As described in the original study, sociodemographic and clinical history data were collected from all patients [7]. PD motor severity was assessed using the MDS Unified Parkinson's Disease Rating Scale–Part III (MDS-UPDRS-III) and the Hoehn and Yahr (H&Y) scale. Clinical evaluation was performed in the "ON state" under the effect of habitual dopaminergic therapy. The individual levodopa equivalent daily dose (LEDD, milligrams per day) was calculated for each patient using the conventional formula [13, 14].

The NMSS was used to assess nonmotor disturbances. The NMSS includes 30 items grouped into the following nine domains: cardiovascular (two items), sleep/fatigue (four items), mood/cognition (six items), perceptual problems/hallucinations (three items), attention/memory (three items), gastrointestinal tract (three items), urinary (three items), sexual function (two items), and miscellaneous (four items). The assessment period referred to "the past month." Each item score results from the product of severity (0–3) and frequency (1–4) ratings, allowing the scale to capture symptoms that are severe but relatively infrequent or less severe but persistent. The total NMSS score ranges from 0 to 360 [15].

The PDQ-39, a self-administered questionnaire, was used to assess the impact of PD on HR-QoL. It contains 39 items covering eight domains: mobility, activities of daily living, emotional well-being, stigma, social support, cognition, communication, and bodily discomfort. The PDQ-39 was designed to capture the frequency of various PD-related problems in patients' daily lives, scored on a 0–4 scale for a maximum possible total score of 156 [10].

Finally, sleep problems were assessed using the PDSS-2, which consists of 15 items investigating various sleep and nocturnal disturbances grouped into five domains: nocturnal movement-related problems (PDSS-2 I), quality of sleep (PDSS-2 II), dreaming distress (PDSS-2 III), fragmentation of sleep (PDSS-2 IV), and insomnia symptoms (PDSS-2 V) [16]. A cutoff of 18/60 has been identified in a European PD population as the threshold above which nocturnal problems are considered clinically significant and warrant further diagnostic workup and treatment [11].

2.4. Ethics Statement. This study was conducted in accordance with the principles of the Declaration of Helsinki. The local ethical committee of the University Hospital of Rome Tor Vergata approved the study.

2.5. Statistical Analysis. Data were analyzed using the IBM SPSS software, Version 27.0.

Descriptive statistics were used to summarize the demographic and clinical characteristics of the sample. Pairwise deletion was applied for missing values. Data were visualized using boxplots and compared using the Kruskal–Wallis test (independent samples and Bonferroni correction). Parametric and nonparametric statistics were reported for all included scales (total score and single domain score). The precision of the scale was determined using the standard error of measurement (SEM). A smaller SEM indicates a more reliable test (a SEM value of < 1/2; the standard deviation was used as a criterion of acceptable precision).

A cutoff score of 18/60 on the PDSS-2 was used to define clinically relevant PD-specific sleep disturbances. PD subjects were divided into two groups to differentiate "poor sleepers" (PDSS-2 total score ≥ 18) from "good sleepers" (PDSS-2 total score < 18) [11]. A cutoff of 50 years for AAO [17] was also used to classify patients into early onset (AAO ≤ 50 years old) and late-onset (AAO > 50 years old) PD.

For group comparisons, independent sample tests were applied. Mann–Whitney *U* tests were used for ordinal variables, while chi-square and Fisher's exact tests were used for categorical variables. The Kruskal–Wallis test for independent samples, with Bonferroni's correction, was applied in cases of multiple comparisons.

Correlations between NMSS, PDQ-39, and PDSS-2 scores and variables of interest were examined using Spearman's rank correlation coefficient rho (rho ≤ 0.3 was considered a weak correlation, rho = 0.3 – 0.59 a moderate correlation, and rho ≥ 0.6 a strong correlation). A probability value of < 0.05 was considered statistically significant, adjusted using the Bonferroni correction for multiple comparisons among total scores.

Missing questionnaire data were considered an indirect measure of data quality and questionnaire acceptability. Data completeness was deemed adequate if more than 95% of the questionnaire responses were fully computable.

No a priori power analysis was conducted; therefore, a post hoc statistical power analysis was performed using G∗ Power software [18]. For the main group comparisons using Mann–Whitney *U* and chi-square tests, with an alpha level of 0.05 and a total sample size of 154, the achieved statistical power ($1-\beta$) exceeded 0.80 for medium to large effect sizes (Cohen's $d \geq 0.5$ and Cramer's $V \geq 0.3$, respectively). For Spearman's correlational analyses, the sample size was adequate to detect medium to strong associations ($\rho \geq 0.3$) with a statistical power greater than 0.80.

3. Results

3.1. Demographic and Clinical Data. This study included an initial cohort of 154 patients with PD, 92 males (59.7%) and 62 females (40.3%) who fulfilled the inclusion criteria; their mean age was 68.79 ± 9.24 years, with a mean disease duration of 6.0 ± 5.12 years, as previously described in the original publication [7].

Distributing patients based on their H&Y stage, 23 patients were included as H&Y Stage 1 (15.1%), 83 as H&Y Stage 2 (54.6%), 30 as H&Y Stage 3 (19.7%), and 16 as H&Y Stage 4 (10.5%). Because only two patients were classified as H&Y Stage 5, they were excluded from the data analysis. At the time of the investigation, 137 patients were receiving dopaminergic therapy, while the remaining 17 were drug-naïve.

Table S1 shows the main demographic and clinical features of the final cohort of 152 patients included in the data analysis.

The main demographic and motor features (age, disease duration, MDS-UPDRS-III, LEDD, and H&Y) did not significantly differ between male and female patients.

The Kruskal–Wallis test by independent samples, followed by Bonferroni correction, showed that the MDS-UPDRS-III score, the mean LEDD values, and disease duration depended on the H&Y stage (1 < 2 < 3, 1 < 4, and 2 < 4; $p < 0.001$).

3.2. NMSS and PDQ-39 Along the Disease Stage. Of the 152 patients included in the study, complete data were available for 100% (152/152) on the NMSS, 99.3% (151/152) on the PDQ-39, and 94.2% (145/152) on the PDSS-2.

Table 1 shows the total and domain-specific scores of the NMSS, PDSS-2, and PDQ-39 for all patients and for subgroups distributed by H&Y stage.

Virtually all patients (151/152) reported at least one NMS (NMSS > 1), with an increasing burden corresponding to motor progression as assessed by the H&Y stage (mean NMSS total scores ranging from 54.64 ± 40.51 at H&Y Stage 1 to 76.06 ± 37.77 at H&Y Stage 4).

When comparing patient subgroups based on H&Y stage (Table 1), we observed that the NMSS total score (Figure 1, Plot A), the "sleep/fatigue" domain (Figure 1, Plot B), and all the NMSS domains except for the "cardiovascular" and the "attention/memory" domains (Table 1) significantly increased with advancing H&Y stage.

Similarly, patients' HR-QoL worsened with increasing H&Y stage, with the exception of the "stigma," "social support," and "cognition" domains (Table 1). Overall, 141 patients (92.76%) reported sleep problems on the PDSS-2, with a very high prevalence across all disease stages, ranging from 86.36% in H&Y Stage 1 to 100% in H&Y Stages 2 and 4 (Table 1).

3.3. Correlation Analyses Among Study Data. Spearman rank correlation coefficients were calculated for all included variables. The results revealed a significant positive correlation between disease duration and LEDD (rho = 0.81, $p < 0.001$), MDS-UPDRS-III (rho = 0.63, $p < 0.001$), and H&Y stage (rho = 0.65, $p < 0.001$).

NMSS total scores showed significant positive correlations with AAO (rho = 0.23, $p = 0.006$), MDS-UPDRS-III (rho = 0.48, $p < 0.001$), H&Y stage (rho = 0.42, $p < 0.001$), LEDD values (rho = 0.32, $p < 0.001$), PDSS-2 total scores (rho = 0.55, $p < 0.001$), and PDQ-39 total scores (rho = 0.69, $p < 0.001$).

Figure 2 shows the significant correlations found between each domain of the NMSS and the PDQ-39.

PDSS-2 total scores significantly correlated with age (rho = 0.33, $p < 0.001$), MDS-UPDRS-III (rho = 0.39, $p < 0.001$), H&Y scale (rho = 0.46, $p < 0.001$), NMSS "cardiovascular" domain (rho = 0.23, $p = 0.006$), NMSS "sleep/fatigue"

TABLE 1: The total and single domain score distributions of the nonmotor symptom scale (NMSS), Parkinson's Disease Sleep Scale-2nd version (PDSS-2), and Parkinson's Disease Questionnaire-39 (PDQ-39) in all patients and when distributed by Hoehn & Yahr (H&Y) stage. Data are expressed as mean ± standard deviation.

	All	Disease stage (H&Y scale)				*p*	Pairwise comparison
		I	II	III	IV		
NMSS domains	$N = 152$	$N = 23$	$N = 83$	$N = 30$	$N = 16$		
NMSS cardiovascular	1.68 ± 3.3	2.48 ± 4.98	1.19 ± 2.60	1.97 ± 3.21	2.56 ± 3.72	0.335	NA
NMSS sleep/fatigue	11.05 ± 9.99	4.52 ± 3.41	11.13 ± 9.93	14.97 ± 11.78	12.63 ± 9.01	0.001	I < II; I < III; I < IV
NMSS mood/cognition	11.78 ± 14.09	4.83 ± 8.50	11.25 ± 13.99	16.33 ± 16.30	15.94 ± 13.22	0.001	I < III; I < IV
NMSS perceptual problems/ hallucinations	0.84 ± 2.36	0 ± 0.00	0.69 ± 2.24	1.20 ± 2.14	2.13 ± 4.05	0.009	I < III; I < IV
NMSS attention/memory	4.16 ± 7.28	3.09 ± 6.57	4.00 ± 7.48	5.60 ± 8.06	3.81 ± 5.75	0.240	NA
NMSS gastrointestinal tract	3.86 ± 4.39	2.26 ± 3.31	3.36 ± 4.20	5.23 ± 3.84	6.13 ± 6.21	0.008	I < III
NMSS urinary	11.10 ± 9.94	3.91 ± 5.30	10.65 ± 10.05	15.37 ± 8.96	15.75 ± 10.30	0.001	I < II; I < III; I < IV; II < III
NMSS sexual function	3.72 ± 5.30	1.22 ± 2.73	2.76 ± 4.22	6.47 ± 6.92	7.19 ± 6.25	0.001	I < III; I < IV; II < IV
NMSS miscellaneous	6.47 ± 6.32	3.91 ± 4.76	5.05 ± 5.33	10.50 ± 7.09	9.94 ± 7.09	0.001	I < III; I < IV; II < III; II < IV
NMSS total score	54.64 ± 40.51	26.22 ± 24.89	50.08 ± 36.57	77.63 ± 46.14	76.06 ± 37.77	0.001	I < II < III, IV
PDSS-2 domains	$N = 145$	$N = 22$	$N = 78$	$N = 29$	$N = 16$		
PDSS-2 motor symptoms	4.03 ± 4.2	2.09 ± 2.84	3.71 ± 4.00	5.48 ± 4.8	5.69 ± 4.8	0.007	I < III; I < IV
PDSS-2 sleep quality	2.69 ± 2.22	1.23 ± 1.79	2.71 ± 2.00	3.62 ± 2.53	2.94 ± 2.35	0.002	I < II; I < III; I < IV
PDSS-2 dream distressing	1.61 ± 2.32	0.77 ± 1.07	1.33 ± 1.99	1.52 ± 1.84	4.31 ± 3.74	0.002	1 < IV; II < IV; III < IV
PDSS-2 fragmented sleep	6.77 ± 3.36	3.23 ± 2.58	6.50 ± 2.74	9.21 ± 2.94	8.50 ± 3.31	0.001	I < II < III; I < IV
PDSS-2 insomnia symptoms	1.74 ± 2.18	1.59 ± 2.02	1.44 ± 1.90	2.52 ± 2.59	2.06 ± 2.64	0.272	NA
PDSS-2 total	16.85 ± 9.79	8.91 ± 7.48	15.68 ± 7.59	22.34 ± 10.43	23.50 ± 11.78	0.001	I < II < III; I < IV
PDQ-39 domains	$N = 152$	$N = 23$	$N = 83$	$N = 30$	$N = 16$		
PDQ-39 mobility	12.53 ± 11.39	2.87 ± 4.13	9.14 ± 7.80	22.00 ± 11.23	26.25 ± 10.88	0.001	I < II < III; I < IV; II < IV
PDQ-39 ADL	6.07 ± 5.86	2.09 ± 2.76	4.57 ± 4.18	10.60 ± 6.41	11.06 ± 7.42	0.001	I < II < III; I < IV; II < IV
PDQ-39 emotional well-being	8.31 ± 4.96	4.43 ± 3.20	8.27 ± 4.54	10.37 ± 5.65	10.25 ± 4.74	0.001	I < II, III, IV
PDQ-39 stigma	2.64 ± 3.26	2.70 ± 3.21	2.24 ± 3.13	3.10 ± 3.31	3.81 ± 3.76	0.283	NA
PDQ-39 social support	0.58 ± 1.48	0.26 ± 0.75	0.61 ± 1.69	0.83 ± 1.53	0.38 ± 0.88	0.580	NA
PDQ-39 cognition	3.26 ± 3.08	1.87 ± 1.79	3.23 ± 3.08	4.03 ± 3.46	4.00 ± 3.29	0.064	NA
PDQ-39 communication	1.80 ± 2.28	0.91 ± 1.56	1.53 ± 2.12	2.33 ± 2.35	3.44 ± 2.94	0.004	I < IV; II < IV
PDQ-39 bodily discomfort	3.98 ± 2.87	2.78 ± 2.43	3.64 ± 2.72	5.40 ± 2.84	4.81 ± 3.23	0.004	I < III; II < III
PDQ-39 total	39.17 ± 25.26	17.91 ± 13.77	33.23 ± 18.39	58.67 ± 26.49	64.00 ± 25.16	0.001	I < II < III; I < IV; II < IV

Note: $p < 0.05$ Kruskal–Wallis, independent samples, and Bonferroni correction.

domain (rho = 0.56, $p < 0.001$), NMSS "mood/cognition" domain (rho = 0.28, $p = 0.001$), NMSS "perceptual problem/ hallucination" domain (rho = 0.28, $p = 0.001$), NMSS "attention/memory" domain (rho = 0.34, $p < 0.001$), NMSS "gastrointestinal tract" domain (rho = 0.29, $p < 0.001$), NMSS "urinary" domain (rho = 0.44, $p < 0.001$), NMSS "sexual function" domain (rho = 0.17, $p = 0.004$), NMSS "pain" item (rho = 0.34, $p < 0.001$), NMSS "hyposmia" item (rho = 0.25, $p = 0.002$), NMSS "sweating" item of the "miscellaneous" domain (rho = 0.20, $p = 0.016$), and NMSS total scores (rho = 0.55, $p < 0.001$).

PDSS-2 total scores significantly correlated with PDQ-39 total scores (rho = 0.63, $p < 0.001$).

The PDQ-39 total score correlated with the PDSS-2 "fragmented sleep" domain (rho = 0.53, $p < 0.001$), the PDQ-39 "mobility" domain correlated with the PDSS-2 "fragmented sleep" domain (rho = 0.54, $p < 0.001$), the PDQ-39 "mobility" domain correlated with the PDSS-2 total

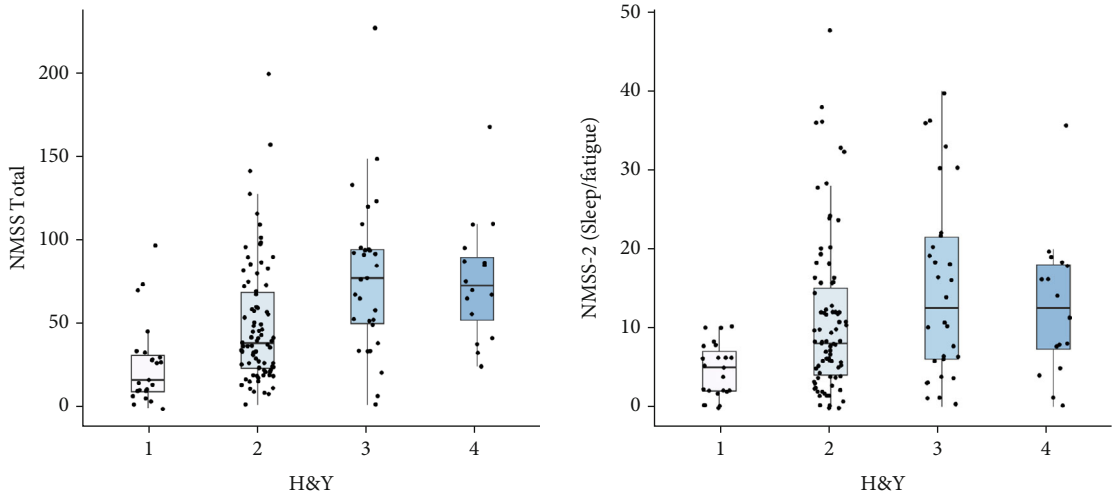

FIGURE 1: Graphical representation of mean score of NMSS total score (Plot A, 1 < 2 < 3,4) and NMSS sleep/fatigue domain (NMSS-2) score (Plot B, 1<2, 1,2<3, 1,2<4) according to the H&Y stage.

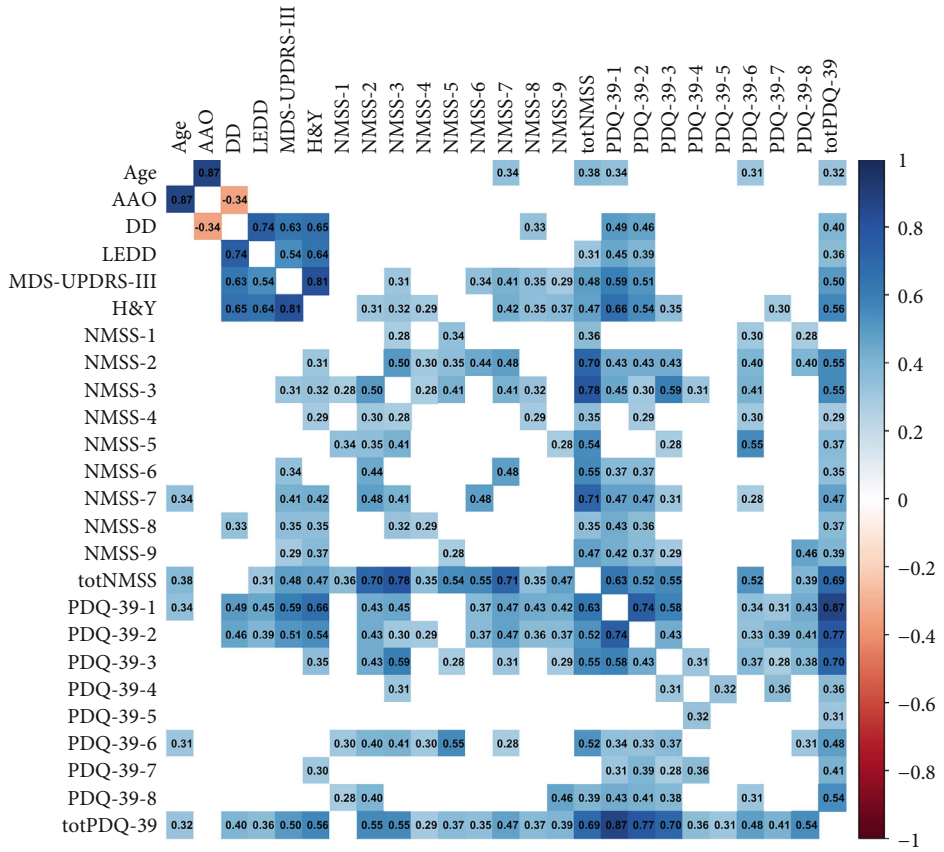

FIGURE 2: Correlation matrix showing the significant positive (blue) Spearman correlation coefficients (rho) between each domain of the nonmotor symptom scale (NMSS) and the Parkinson's Disease Questionnaire-39 (PDQ-39) using the Bonferroni correction. *AAO*, age at onset; *DD*, disease duration; *LEDD*, levodopa equivalent dose (milligrams per day); *MDS-UPDRS-III*, Movement Disorder Society Unified Parkinson's Disease Rating Scale–motor section; *H&Y*, Hoehn & Yahr scale.

score (rho = 0.57, $p < 0.001$), and the PDQ-39 "bodily discomfort" domain correlated with the PDSS-2 "motor symptom" domain (rho = 0.56, $p < 0.001$).

The H&Y stage significantly correlated with the PDQ-39 "mobility" domain (rho = 0.66, $p < 0.001$) and with the PDQ-39 total score (rho = 0.59, $p < 0.001$).

Age significantly correlated with the PDQ-39 total score (rho = 0.27, $p < 0.001$), as well as with the PDQ-39 "cognition" (rho = 0.31, $p < 0.001$) and "mobility" (rho = 0.34, $p < 0.001$) domains.

3.4. Comparison Analyses Between EOPD and LOPD Patients. When comparing EOPD patients (AAO ≤ 50 years, $n = 16$) and LOPD patients ($n = 126$), a significant difference in disease duration emerged between the two groups (9.43 years vs. 5.58 years, $t = 2.88$, $p < 0.001$).

EOPD and LOPD patients displayed similar motor impairment as assessed by the H&Y stage (2.1 ± 0.8 vs. 2.3 ± 0.8, respectively) and the MDS-UPDRS-III (24.52 ± 11.7 vs. 24.88 ± 16.19, respectively). However, when using disease duration as a covariate, a statistically significant difference emerged in both the H&Y stage and the MDS-UPDRS-III, with higher values in LOPD ($F = 13.37$, $p < 0.001$ and $F = 5.37$, $p = 0.022$, respectively).

Conversely, EOPD patients showed lower NMSS total scores compared to LOPD (37.88 ± 36.41 vs. 54.18 ± 39.65, $F = 4.33$, $p = 0.03$), but similar PDQ-39 total scores (34.43 ± 31.19 vs. 39.14 ± 24.85).

Regarding NMSS domains, EOPD patients had lower scores in the "cardiovascular" (1.18 ± 0.3 vs. 3.059 ± 0.23, $t = -2$ to 19, $p < 0.034$), "perceptual problems/hallucinations" (0.19 ± 0.54 vs. 0.83 ± 2.38, $t = -2.53$, $p = 0.013$), and "attention/memory" domains compared to LOPD patients (4.1 ± 7.41 vs. 3.12 ± 4.13, $t = -3.78$, $p < 0.001$); using disease duration as a covariate, EOPD patients also showed lower scores in the "urinary" domain ($F = 3.61$, $p = 0.05$) and in the "hyposmia" item of the "miscellaneous" domain ($F = 4.35$, $p = 0.039$) compared to LOPD patients.

No differences emerged in PDQ-39 domain scores between the two groups.

Again, no differences emerged in LEDD between the two groups.

Regarding sleep, EOPD patients had lower PDSS-2 total scores (13.06 ± 12.38 vs. 17.4 ± 9.52, $F = 7.74$, $p = 0.006$) and lower scores in the "fragmented sleep" domain (4.88 ± 4.24 vs. 6.98 ± 3.19, $F = 16.87$, $p < 0.001$) compared to LOPD patients. No other significant differences were found. Finally, a higher proportion of LOPD patients were classified as "poor sleepers" compared to EOPD (51/123, 41.5%, vs. 4/16, 25%); however, the difference did not reach statistical significance. Figure 3 summarizes the main clinical differences found between EOPD and LOPD patients.

3.5. Comparison Analyses Between Poor Sleepers and Good Sleepers. Considering the PDSS-2 cutoff for diagnosing sleep disorders in patients with PD, we divided the whole group of patients into "good sleepers" (PDSS-2 < 18) and "poor sleepers" (PDSS-2 ≥ 18), and then compared the two groups, adjusting the analysis for age. Fifty-eight patients (39.5%) were classified as "poor sleepers," and 89 patients (60.5%) were included in the "good sleepers" group. "Poor sleepers" had a higher AAO (64.9 ± 10.54 vs. 61.11 ± 10.06, $t = 2.13$, $p = 0.035$), H&Y stage (2.64 ± 0.83 vs. 2.03 ± 0.78, $t = 4.45$, $p < 0.001$), and MDS-UPDRS-III scores (28.8 ± 13.3 vs. 22.2 ± 11.1, $t = 3.02$, $p = 0.002$) than "good sleepers."

Furthermore, "poor sleepers" had higher NMSS total scores (74.98 ± 43.90 vs. 38.04 ± 28.34) compared to "good sleepers." All the domains of the NMSS scale were higher in "poor sleepers" than in "good sleepers," except for the "sexual function" domain and the "sweating" and "weight" items of the "miscellaneous" domain, which did not differ between the two groups.

A mean PDQ-39 total score of 56.02 ± 25.08 was found in "poor sleepers," which was almost double that of "good sleepers" (33.28 ± 19.45). Figure 4 summarizes the most significant clinical differences found between poor and good sleepers.

4. Discussion

In this study, the primary objective was to investigate the impact of NMS on HR-QoL in patients with PD, with a specific focus on disease progression and AAO. The results of the present study expand upon those reported in an earlier analysis of this cohort, specifically examining the impact of sleep disturbances along the course of disease progression.

The present study showed how not only sleep disturbances, but most NMS, profoundly impact the daily life activities of individuals with PD, particularly as the disease progresses clinically in terms of motor manifestations and disease duration.

The increasing burden of nonmotor signs and symptoms with the progression of motor impairment reflects the growing neuropathological load and the accumulation of synucleinopathy across multiple sites within the central and peripheral nervous systems [19]. Consistently, motor fluctuations are associated not only with a higher burden of nonmotor signs and symptoms but also with their fluctuations, which further impair patients' HR-QoL [6].

Our study confirmed the remarkably high prevalence of NMS, starting from the earlier phases of PD (nearly 100% from H&Y 1) and significantly increasing with advancing disease stage. Notably, nearly all the NMS domains investigated by the NMSS scale exhibited a substantial increase parallel to the progression of the H&Y stage.

Among the different domains of NMS, the lack of an increase in prevalence with disease motor progression was evident for cognitive and cardiovascular manifestations. Both findings, although potentially unexpected at first glance, reflect the fact that these manifestations may occur independently of the disease stage and, in the case of cardiovascular symptoms, may be present from the early stages of the disease in those patients who present them [20, 21]. As for cognitive impairment, its apparent stability across stages may be explained by the exclusion of patients with overt cognitive decline. While this criterion was necessary to minimize potential biases related to the questionnaire-based design of the study, it may have limited our ability to capture one of the most disabling features impacting HR-QoL in PD. Alongside the escalation of NMS, the present study also confirmed the significant increase in sleep disturbances [7], evaluated through both the "sleep domain" of the NMSS and the PDSS-2, which correlated with the progression of motor

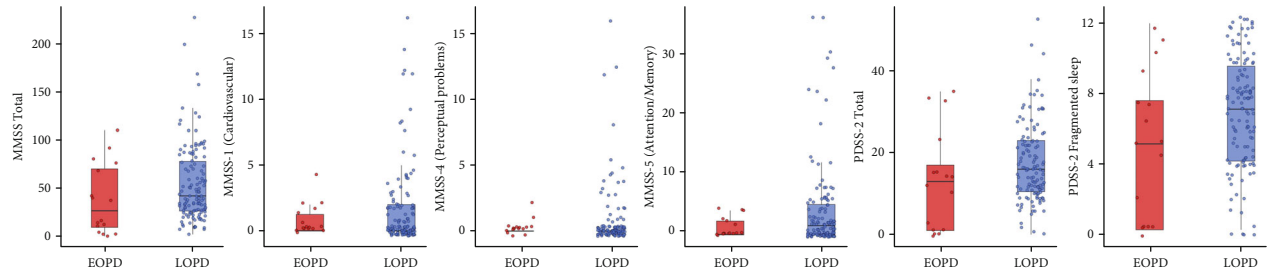

FIGURE 3: Graphical representation of the main clinical differences found between early onset Parkinson's disease (EOPD) patients and late-onset Parkinson's disease patients (LOPD). *NMSS*, nonmotor symptom scale; *PDSS-2*, Parkinson's Disease Sleep Scale-2nd version.

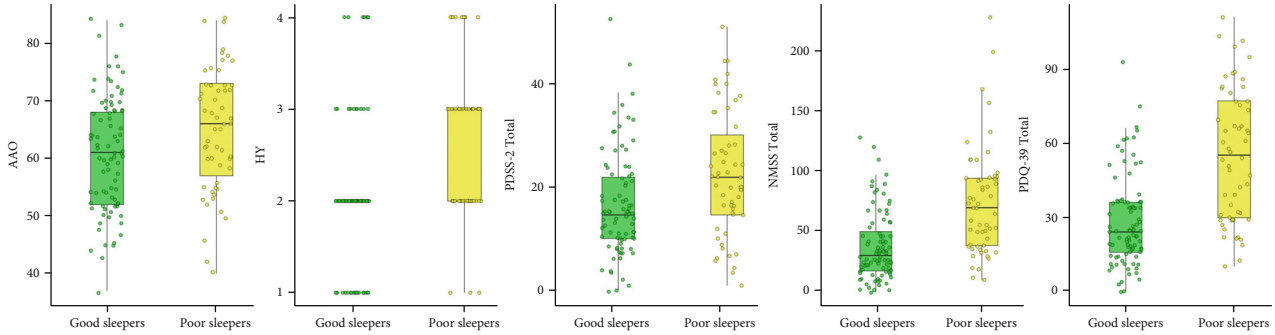

FIGURE 4: Graphical representation of the main clinical differences found between "good sleepers" and "poor sleepers" patients with Parkinson's disease based on the validated cutoff of 18/60 on the PDSS-2. *AAO*, age at onset; *NMSS*, nonmotor symptom scale; *PDQ-39*, Parkinson's Disease Questionnaire-39; *PDSS-2*, Parkinson's Disease Sleep Scale-2nd version.

disturbances, thus suggesting a tight link between sleep issues and motor deterioration [22].

Regarding the PDQ-39 scale, and as expected due to the partial overlap between clinical scales, we similarly found that lower HR-QoL was more common as the disease progressed, reaching a plateau at H&Y Stages 3 and 4.

To further explore the impact of AAO, a comparative analysis of NMS and the PDQ-39 scores was performed between patients diagnosed with EOPD (AAO ≤ 50 years) and those with LOPD (AAO > 50 years). EOPD patients presented a lower burden of NMS and less motor impairment compared to LOPD patients, despite a longer disease duration, confirming that AAO influences several facets of the disease.

Furthermore, not only the burden but also the spectrum of NMS displayed by EOPD patients differed markedly from that observed in LOPD patients. In particular, cardiovascular disturbances, cognitive impairment, visual hallucinations, and sleep disturbances were significantly less common in EOPD patients compared to LOPD patients.

A greater burden of autonomic symptoms, cognitive decline, visual hallucinations, and, most importantly, REM sleep behavior disorder (RBD) is a hallmark of "body-first" PD, possibly suggesting that LOPD patients exhibit a greater α-synuclein deposition in peripheral tissues compared to EOPD patients [23], who, by contrast, appear to show a central origin of the neuropathology ("brain-first" PD subtype), possibly driven by specific genetic bases [24, 25].

Nevertheless, despite differences in motor and NMS burdens, the impact on daily living, as assessed through the PDQ-39 scale, did not significantly differ between the two groups. Indeed, EOPD patients face peculiar challenges in their daily lives due to factors such as occupation, marital and parental responsibilities, and social dynamics, with unique consequences for their HR-QoL [26–28].

As another novel finding of this study, NMS and impaired HR-QoL presented as interconnectionally linked in PD patients, as shown by the significant correlations found between NMSS and PDQ-39 total scores. Specifically, the overall NMS burden correlated with nearly all the domains of the PDQ-39 scale, indicating that the presence of NMS significantly contributes to the reduction of almost every aspect of HR-QoL in PD [29]. In particular, the strongest correlations were observed between the broad spectrum of NMS and the PDQ-39 domains of "mobility," "activity of daily living," and "cognition."

While the previous work from our group has extensively addressed the relationship between sleep disturbances and HR-QoL, in the present study, we focused on the differential impact of AAO and the association of clinically relevant sleep issues with a broader range of nonmotor features. We included sleep disturbances in the analysis due to their relevance within the NMS spectrum and found that "poor sleepers" (PDSS-2 ≥ 18) [11] exhibited a higher burden of NMS and overall poorer HR-QoL than "good sleepers," irrespective of age, LEDD, and disease duration. Considering that sleep quality and architecture can be associated with motor performance [30], as also postulated by the sleep benefit hypothesis, the improvement of sleep in PD patients further represents a main target for improving HR-QoL and motor disturbances.

This study has several limitations due to its observational and cross-sectional design, which did not allow for longitudinal evaluation of clinical scales over time: its questionnaire-based design, which may be subject to recall bias or subjective symptom interpretation, depending on whether the scales were completed by patients alone or with their family members; the absence of polysomnographic confirmation of sleep disturbances, potentially leading to underestimation or overestimation of their prevalence and severity; and finally, the lack of genetic testing, which limits our understanding of the role of genetic factors in the observed differences between EOPD and LOPD patients.

Further studies involving larger patient cohorts are needed to better understand the relationship between NMS and HR-QoL in PD and to validate the findings of this study. Additionally, longitudinal studies could provide valuable insights into the long-term effects of nonmotor signs and symptoms on patients' well-being and help determine the effectiveness of interventions targeting these features. Finally, dedicated studies involving additional clinical scales and broader assessments should explore the relationship between specific PD features, nonmotor signs and symptoms, and HR-QoL, such as the intricate interplay between posture, mood, and cognition [31].

5. Conclusions

This study expanded upon previously published results [6] by documenting how nonmotor signs and symptoms significantly impact patients' overall HR-QoL along with disease progression and differently based on AAO, highlighting the need to address such modifiable factors to alleviate the increasing burden of the disease and possibly pave the way for tailored treatment decisions.

Data Availability Statement

The datasets generated during analysis are available from the corresponding author upon reasonable request.

Conflicts of Interest

The authors declare no conflicts of interest.

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The authors have nothing to report.

Supporting Information

Additional supporting information can be found online in the Supporting Information section. *(Supporting Information)* Table S1: The main demographic and clinical features of the final cohort of 152 patients included in the data analysis.

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