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## **Systematic assessment of autonomic symptoms in restless legs syndrome**

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## **Abstract**

**Objectives:** To compare the clinical features of autonomic dysfunction using the SCOPA-AUT questionnaire in untreated patients with restless legs syndrome (RLS) with controls, to identify factors associated with more severe autonomic symptoms, and to assess the effect of medication in patients.

**Methods:** The SCOPA-AUT questionnaire that evaluates cardiovascular, gastrointestinal, urinary, thermoregulatory, pupillomotor, and sexual dysfunctions was completed by 409 consecutive untreated patients with RLS ( $54.1 \pm 14.5$  y.o; 265 women) and 331 controls ( $59.0 \pm 17.0$ ; 161 women). Clinical and polysomnographic data were assessed in all patients. A subgroup of 57 patients were evaluated a second time after treatment (mostly dopaminergic agonist) after an interval of  $0.88 \pm 1.42$  year.

**Results:** Compared to controls, untreated patients with RLS were younger, more often women, obese, with increased cardiovascular diseases (CVD). The SCOPA-AUT total score was higher in patients than controls in unadjusted and adjusted models. Patients had more autonomic symptoms in all subdomains of the scale (except for sexual dysfunction in men). These results were confirmed in a subgroup of 259 cases and age-sex-matched controls. Female gender, obesity, RLS severity, diabetes mellitus, CVD, sleepiness, insomnia and depressive symptoms but neither periodic legs movements during sleep (PLMS) nor objective sleep parameters were associated with high scores. Despite RLS and PLMS improvement, medication did not change total and subdomain scores.

**Conclusions:** Patients with RLS have frequent and large spectrum of autonomic symptoms, without effect of PLMS, sleep fragmentation and medication. These results suggest a global autonomic dysfunction in RLS that should be assessed more systematically in severe patients.

**Keywords :** Restless legs syndrome, Autonomic dysfunction, Periodic leg movements, SCOPA-AUT, cardiovascular diseases

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## INTRODUCTION

Restless legs syndrome (RLS) is a common neurological sensori-motor disorder that impairs sleep and quality of life.<sup>1,2</sup> Periodic limb movements during sleep (PLMS) and sleep fragmentation are observed in up to 80% of patients with RLS.<sup>3</sup> Several studies reported associations between RLS, hypertension, and cardiovascular diseases (CVD).<sup>4-6</sup> However, these relationships remain controversial and the underlying mechanisms are still unclear.<sup>7-11</sup> Recent findings also highlighted the links between PLMS, nocturnal blood pressure (BP) and heart rate (HR) elevations, frequent systolic non-dipper profile, sympatho-vagal imbalance during wakefulness and sleep, and increased BP during evening wakefulness associated with sensory discomfort in patients with RLS.<sup>12-19</sup> All these findings may support the long-term increased risk for CVD morbidity and mortality in these patients.<sup>11</sup>

The activity of the autonomic nervous system is largely influenced by wakefulness and sleep.<sup>20</sup> Hence, sleep disorders are often associated with impaired cardiovascular autonomic control and sympatho-vagal imbalance.<sup>10,20</sup> Cardiovascular autonomic symptoms (i.e. tachycardia, bradycardia, abrupt changes in BP) have also been reported in RLS.<sup>14,15</sup> Few small scale studies used the well-standardized Scale for Outcomes in Parkinson's Disease – autonomic dysfunction (SCOPA-AUT) questionnaire, and reported clinical autonomic dysfunctions in RLS on cardiovascular, gastrointestinal, urinary, thermoregulatory, pupillomotor and sexual domains.<sup>21-23</sup> However, these studies need to be replicated, because of discrepancies in their results due to the differences in populations, treatment intake, sample size, confounding factors and study design. Moreover, none of these studies assessed patients with RLS with a polysomnography (PSG) to study the impact of sleep disturbances and PLMS on autonomic symptoms. Whether the cardiovascular and other clinical autonomic dysfunctions are related to RLS per se, sleep fragmentation, PLMS, medications or other confounding factors remain unknown.

The objectives of this study were (1) to evaluate autonomic symptoms using the validated SCOPA-AUT questionnaire in a large sample of untreated patients with RLS and controls taking into account potential confounders, (2) to identify clinical, biological and polysomnographic factors associated with a high SCOPA-AUT total and cardiovascular scores in RLS and (3) to assess longitudinally the effect of medication on autonomic symptoms in RLS.

## **METHODS**

### **Participants**

Four hundred and nine consecutive untreated adult patients with RLS (mean age  $54.13 \pm 14.48$  y.o., 265 women (64.79%)) were recruited from 2014 to 2019 in the sleep-wake disorder unit, Department of neurology, Gui de Chauliac Hospital, Montpellier, France. The RLS diagnosis was made by physicians trained in sleep disorders using the International Restless Legs Syndrome Study Group criteria.<sup>1</sup> Patients with clinically significant renal, neurodegenerative or inflammatory disorders, conditions potentially comorbid with RLS, were excluded. Patients with RLS treated with drugs known to alleviate (dopamine agonists, alpha2delta ligand, opioids, benzodiazepine, z-drugs) or worsen RLS (neuroleptics, antidepressants, sedative antihistaminics) stopped their treatment for at least two weeks before study inclusion whereas 143 (34.96%) were drug naive. RLS severity was evaluated at study inclusion in untreated condition, with the International Restless Legs Syndrome Study Group (IRLSSG) questionnaire (scores from 10 to 20 indicate moderate; 20 to 30 severe; 30 to 40 very severe RLS symptoms), with all patients having score  $>15$ .<sup>24</sup> Age at RLS onset and family history of RLS were also recorded.

Three hundred and thirty one adults (mean age  $58.98 \pm 17.03$  y.o., 161 women (48.64%)) were recruited during the same period from the general population through advertisements and local association network to participate in the study. Inclusion criteria were: normal neurological examination, absence of sleep complaints, normal and regular sleep schedule, and absence of present or past personal history of RLS. Exclusion criteria were: history of clinically significant renal, neurodegenerative or inflammatory disorders, and any psychotropic drugs intake including dopamine agonists, alpha2delta ligand, opioids, neuroleptics, antidepressants, or sedative antihistaminics.

All participants could speak and understand French. To avoid potential bias, no details were given to participants about the exact objectives of this study. The methods were carried out in accordance with the approved guidelines. This study was approved by the institutional review board of the University of Montpellier, France. All participants consented to participate in the study.

### **Clinical autonomic dysfunction**

Autonomic symptoms were evaluated by the SCOPA-AUT, a 25-item self-questionnaire that assesses gastrointestinal (7 items), urinary (6 items), cardiovascular (3 items), thermoregulatory (4 items), pupillomotor (1 item) and sexual function (2 items).<sup>25</sup> Each item assesses the frequency of one autonomic symptom within the past month (6 months for syncope) and provides a four-point Likert scale (from 0=never to 3=often). The SCOPA-AUT total score ranges from 0 to 69, with the highest score reflecting worse autonomic functioning.

### **Demographic, clinical, sleep and biological characteristics**

All participants had a semi-structured evaluation including demographic characteristics and personal history of chronic diseases assessment. A homemade structured questionnaire recorded the presence of cardiovascular comorbidities, defined as the presence of diabetes type 2, hypertension, dyslipidemia, or CVD (i.e. coronary artery disease, chronic heart failure, arrhythmia and stroke). All medications taken during the previous month were detailed together with their dose and age at intake onset. Subjects receiving antihypertensive, antiarrhythmic, antidiabetic and lipid-lowering medications were classified as having these conditions.

Patients with RLS also completed the Beck Depression Inventory,<sup>26</sup> a 21-item self-assessment questionnaire (scores between 14 and 19 indicated mild and >19 moderate to severe depressive symptoms), the Epworth Sleepiness Scale (ESS) to evaluate daytime sleepiness (scores >10 indicated excessive daytime sleepiness (EDS))<sup>27</sup> and the Insomnia Severity Index (ISI), a 7-item self-report scale on subjective insomnia symptoms (scores  $\geq 14$ , moderate to severe insomnia).<sup>28</sup>

Serum ferritin levels were measured for all RLS patients by electrochemiluminescence immunoassay (Elecsys, ECLIA, Cobas; Roche Diagnostics International Ltd, Switzerland).

### **Polysomnography**

All patients with RLS in untreated condition (i.e. 266 patients stopped their treatment known to alleviate or worsen RLS for at least two weeks before the study), underwent one-night PSG recording in the sleep laboratory, including electroencephalogram channel (C3/A2, C4/A1, O2/A1), electrooculography, chin electromyography (EMG) and electrocardiogram. Respiration was monitored with a nasal cannula/pressure transducer system, mouth thermistor, chest and abdominal

bands, and pulse oximeter. Leg movements were evaluated with surface EMG electrodes placed on the right and left anterior tibialis muscles. Sleep stages (N1, N2, N3 and REM sleep) were scored manually as well as micro-arousals, PLMS, PLMS associated with micro-arousals (PLMA), periodic leg movements during wakefulness (PLMW) and respiratory events (apnea hypopnea index, AHI) according to standard criteria.<sup>29,30</sup> None of the controls underwent a PSG recording.

### **Longitudinal assessment**

A subgroup of 57 patients with RLS was systematically reassessed in routine care with a second clinical and PSG evaluation under medication for RLS after a mean interval of  $0.88 \pm 1.42$  year. Most were under single-therapy: 48 (82.76%) treated with a dopaminergic agonist (DA), one (1.72%) with opioid and one (1.72%) with alpha2delta ligand. Five (8.62%) had DA and alpha2delta ligand, one (1.72%) DA and opioid, and one (1.72%) DA and clonazepam.

### **Statistical analysis**

Continuous variables were expressed as mean and standard deviation (SD) and categorical variables as number and percentage. Patients with RLS and controls were compared using univariate logistic regression models. Demographic and clinical variables associated with RLS in univariate analyses (with  $p < 0.15$ ) were included in logistic regression models to estimate the adjusted odds-ratio (OR) and their 95% confidence intervals (CI) for the associations between SCOPA-AUT dimension and RLS. Analyses of the patients' clinical, biological and polysomnographic determinants of severe autonomic symptoms was conducted using logistic regression models. As SCOPA-AUT score was skewed using Shapiro-Wilk test, the variable had been dichotomized using the highest tertile as a cutoff. A sensitivity analysis was performed with RLS patients matched with controls according to gender, age ( $\pm 5$  years), BMI ( $\pm 5$  kg/m<sup>2</sup>) and CVD history. To compare the evolution of different parameters between two related groups (i.e. groups evaluated twice in untreated/treated conditions), dependent t-test were used for continuous variables and Cohen's Kappa coefficient or McNemar's test for categorical variables.

Significance level was set at  $p < 0.05$ . Analyses were performed using SAS (version 9.4; SAS Inc., Cary, North Carolina).

## **RESULTS**



Among the 409 patients, the mean age of RLS onset was  $38.33 \pm 16.38$  with a mean disease duration of  $16.02 \pm 12.97$  years, and a family history of RLS was reported by 152 (39.79%) patients. According to the IRLSSG questionnaire, moderate, severe and very-severe RLS symptoms were reported by 94 (22.98%), 197 (48.17%) and 118 (28.85%) patients respectively. Mean ESS score was  $11.34 \pm 5.50$  with 226 (55.67%) reporting EDS (ESS>10). Mean ISI score was  $18.49 \pm 4.72$  and 333 (81.82%) had significant insomnia symptoms. Mean BDI score was  $16.67 \pm 9.99$  with 98 (24.26%) and 132 (32.67%) patients having moderate and severe depressive symptoms, respectively. The mean ferritin level was  $156.27 \pm 117.25 \mu\text{g/l}$  and 61 (16.18%) had a low level (<50 $\mu\text{g/l}$ ).

PSG recording revealed a mean total sleep time at  $333.03 \pm 98.19$  minutes, sleep efficacy at  $69.60\% \pm 19.09$ , wake time after sleep onset at  $100.81 \pm 71.66$  minutes, and PLMW, PLMA and PLMS indexes at  $34.99/\text{h} \pm 34.33$ ,  $14.36/\text{h} \pm 27.85$  and  $40.13/\text{h} \pm 51.58$ , and 223 (56.89%) patients had PLMS index > 15/hour and 75.26% for PLMS>5/hour. Mean apnea-hypopnea index was  $11.54/\text{h} \pm 15.79$ , with 96 (24.49%) patients had AHI > 15h. The mean oxygen saturation was  $94.98\% \pm 2.34$  and the mean micro-arousal index was  $27.26 \pm 29.39/\text{h}$ .

Compared to controls, untreated patients with RLS were younger, more often women, overweight/obese with more CVD (**Table 1**). Subsequent analyses were thus adjusted for these factors.

### **SCOPA-AUT scores in untreated RLS and controls**

Patients with RLS had a higher SCOPA-AUT total score than controls (**Table 2**). Two hundred and three patients (49.6%) and 45 controls (13.6%) had a score  $\geq 16$  (i.e. the highest tertile of the whole population) ( $p < 0.0001$ ). When divided in tertiles the SCOPA-AUT total score was associated with RLS in a dose response fashion even after adjustment for age, gender, BMI and CVD (**Table 2**). Patients with RLS experienced more autonomic problems in all the six subdomains of the scale, with significant differences between groups in unadjusted and adjusted models, except for sexual dysfunction in men (**Table 2**). Accordingly, the frequency of RLS patients with a SCOPA-AUT score greater than zero was also higher than controls in every subdomain, even after adjustments, except for sexual dysfunction in men. We found that 54.8% of patients reported symptoms consistent with autonomic cardiovascular dysfunctions, 86.3% with gastrointestinal, 95.8% with urinary, 90.5% with thermoregulatory, 69.7% with pupillomotor, and from 43.6% (in men) to 75.6% (in women) for

sexual dysfunctions (**Table 2**). Moreover, the frequencies of patients with a score greater than zero for each of the 25 items of the scale was significantly higher than controls for 22 items, with similar trend for syncope (item 16,  $p=0.05$ ), and exception for 2 items related to sexual dysfunction in men (**Table 3**).

In a sensitivity analysis, 259 RLS patients were matched with 259 controls according to gender, age, BMI and CVD history. We confirmed a higher SCOPA-AUT total score ( $15.8\pm 8.0$  vs  $8.0\pm 5.7$ ,  $p<0.0001$ , for patients with RLS and controls respectively) and in all the six subdomains of the scale ( $p<0.001$ ) except for the SCOPA sexual domain in men.

Another sensitivity analysis found no differences in the SCOPA-AUT score between drug-naïve and drug-free patients who stopped treatment at least two weeks before entering the study (**Table 4**). On the other hand, several differences between the groups could be noted on the socio-demographic, clinical and polysomnographic data (**Table 5**).

### **Factors associated with high SCOPA-AUT score in untreated RLS**

Patients with the highest SCOPA-AUT total scores ( $\geq 19$ , i.e. the highest tertile of the SCOPA-AUT total score in patients with RLS) were more often women and overweight/obese. They had higher RLS severity, more often diabetes mellitus, CVD, sleepiness, insomnia and depressive symptoms, and longer sleep latency on PSG, even after adjustment for gender or gender and age (**Table 6**), or further adjustment for BDI score (data not shown). In contrast, no association was found with age at RLS onset, disease duration, PLMS, PLMA, PLMW, sleep fragmentation, AHI, and serum ferritin levels assessed continuously or by category.

Patients with the highest SCOPA-AUT cardiovascular scores ( $\geq 2$ , i.e. the highest tertile of the SCOPA-AUT cardiovascular subscore in patients with RLS) were younger. They had higher RLS severity, more frequent CVD, sleepiness, insomnia and depressive symptoms, even after adjustment for age, with similar tendency for lower ferritin levels (**Table 7**). We confirmed the absence of association between PLMS, PLMA, PLMW, sleep fragmentation, AHI, and SCOPA-AUT cardiovascular subscore.

### **Effect of RLS treatment on autonomic symptoms**

In the subgroup of 57 patients (mean age 58.42y.o  $\pm$ 11.42 at baseline, 61.4% women) evaluated twice in untreated and treated conditions (96.5% with a dopaminergic agonist), improvement were found on RLS severity (IRLSSG mean scores 28.8  $\pm$ 5.7 vs 19.9  $\pm$ 8.8,  $p$ <0.0001), insomnia symptoms (ISI mean scores 19.5  $\pm$ 4.4 vs 14.3  $\pm$ 6.6,  $p$ <0.0001), sleep efficiency (66.6  $\pm$ 18.6 vs 73.9  $\pm$ 16.6%,  $p$ =0.005), wake time after sleep onset (125.2  $\pm$ 68.5 vs 86.8  $\pm$ 59.9 min,  $p$ <0.0003), PLMS (74.6  $\pm$ 54.4 vs 22.3  $\pm$ 39.9/h,  $p$ <0.0001), PLMA (33.5  $\pm$ 36.3 vs 9.5  $\pm$ 17.6/h,  $p$ <0.0001), PLMW (42.9  $\pm$ 33.6 vs 28.4  $\pm$ 33.4/h,  $p$ <0.002) from untreated to treated condition. However, the SCOPA-AUT total score and each subdomain of the scale did not differ significantly between groups (Total score: 14.28 $\pm$ 10.32 vs 13.58 $\pm$ 9.36,  $p$ =0.37, for untreated and treated patients respectively).

## DISCUSSION

In this large case-control study, we found that patients with RLS reported higher frequency of autonomic symptoms assessed with the SCOPA-AUT questionnaire in all the explored domains that include the cardiovascular, gastrointestinal, urinary, thermoregulatory, pupillomotor and sexual functions (for women only), even after adjustment for confounding factors. Higher autonomic scores were associated with female gender, obese/overweight, with higher RLS severity, sleepiness, insomnia and depressive symptoms, diabetes mellitus, CVD, without key effects of the RLS drugs. PLMS and sleep fragmentation were not associated with higher SCOPA-AUT total and cardiovascular scores.

We used the SCOPA-AUT scale, a validated tool initially developed for Parkinson's disease<sup>24</sup> that includes items considered relevant by patients and specialists to assess the dysautonomic-related complaints in multiple domains. The SCOPA-AUT scale was further used in several sleep disorders, REM sleep behavior disorder, OSA, narcolepsy and RLS.<sup>21-23,31-33</sup> Interestingly, mean SCOPA-AUT total scores of patients with RLS in our study are in the same range as other sleep disorders and previous RLS studies.<sup>21-23,32,33</sup> Indeed, using this questionnaire, three RLS case-control studies on small samples reported robust differences for the cardiovascular domain but inconsistent alterations in gastrointestinal, urinary, thermoregulatory, pupillomotor and sexual domains.<sup>21-23</sup> We may also question if all subdomains of the scale are equally relevant and clinically significant for patients with RLS. Some items and subdomains could be relevant in their daily life and management while others may be less crucial in clinical practice, but important for research to report all clinical autonomic dysfunction. Based on the previous studies,<sup>21-23</sup> the results did not allow to conclude on significant

clinical autonomic impairment in RLS and especially on their determinants. In contrast, the present study included a large population of well-characterized consecutive untreated patients with moderate to very-severe RLS, with clinical and PSG assessment to compare autonomic symptoms with a control group taking into account potential confounders, and to study the clinical, biological and neurophysiological factors associated with autonomic symptoms in RLS.

We highlighted a frequent and large spectrum of clinical autonomic dysfunctions in RLS, with impairment in the cardiovascular domain, but also in all other subdomains of the SCOPA-AUT questionnaire, except the sexual area for men. Unexpectedly, we found that women (and not men) with RLS had more sexual autonomic problems than controls. This finding remains controversial in the literature, potentially related to the selected sample, from clinic to general population, and to the instrument used for its assessment.<sup>34,35</sup> All the remaining symptoms may relate to impaired autonomic control of the sympatho-vagal system already reported during sleep and wakefulness in RLS.<sup>20</sup> One of the goals of our study was to investigate the factors associated with high SCOPA-AUT score in RLS patients. Whether the frequency and severity of autonomic symptoms were due to RLS *per se*, sleep fragmentation, PLMS, medication, or other confounding factors, were unknown before this study. We found here that patients with the highest SCOPA-AUT total scores were more often women, obese/overweight, with diabetes mellitus, CVD, with more severe RLS, sleepiness, insomnia and depressive symptoms. We confirmed the association between RLS severity and high SCOPA-AUT score despite the adjustment for depressive symptoms. Same predictors were found for the highest SCOPA-AUT cardiovascular score except for gender and BMI. In contrast, we found no association between SCOPA-AUT total or cardiovascular scores, and RLS disease duration, age at RLS onset, sleep architecture and continuity (except for sleep onset latency), neither with PLMS, PLMA, PLMW and AHI indexes. These findings were unexpected knowing the strong relationship between PLMS, sympathetic activation, and the relative decreased and increased sympathetic activities in slow wave sleep and REM sleep respectively.<sup>36</sup> Moreover, patients with RLS had a sleep-stage dependent sympatho-vagal dysfunction towards a predominant sympathetic activation during slow wave sleep.<sup>16</sup> A recent RLS study underlined that systolic and diastolic blood pressure increased during the suggested immobilization test in patients with leg discomfort whether associated or not with the motor component during wakefulness (i.e. PLMW).<sup>17</sup>

We questioned whether medication for RLS could modify autonomic symptoms as RLS severity was associated with SCOPA-AUT score. Despite efficacy of RLS medication [mostly DA (96.5%) in this study, but also alpha2delta ligand (10.5%) and opioid (3.5%) given in mono or multi-therapy] on its

severity, sleep efficiency, PLMS, PLMA and PLMW indexes, we found no such effect on the SCOPA-AUT total score and on the different subdomains. Our sample evaluated twice in untreated and treated conditions was relatively small (n=57). A post-hoc power analysis based on our data set suggests that 183 patients would have been necessary to show a significant between-group difference before and after being medicated by a dopaminergic agonist equals to 0.7, a standard deviation of 5.8 and an intra-individual correlation of 0.83 with a 80% statistic power and a 2-sided  $\alpha$  level of 0.05 on the SCOPA-AUT total score. Another study found no differences in autonomic function during wakefulness after 3 months of DA in patients with RLS.<sup>37</sup>

Altogether, these results suggest that autonomic symptoms are more related to RLS than PLMS and may be considered as a trait rather than a state marker. Accordingly, among several mechanisms potentially involved, an elevated sympathetic activity in the RLS may be caused by a disinhibition of intermediolateral columns of spinal cord by the deficient hypothalamic dopaminergic descending pathway.<sup>38</sup> However, RLS is frequently associated with metabolic disturbances, insomnia, sleepiness and depressive symptoms that may also increase the risk of clinical autonomic dysfunction, health-related quality of life, hypertension and CVD. Finally, whether the well-known genetic risk factors for RLS<sup>39</sup> may influence the sympatho-vagal deregulation and autonomic symptoms in RLS remains to be further studied. A significant increased sympatho-vagal balance was found during slow wave sleep in patients with RLS and homozygotes for the risk MEIS1 allele.<sup>16</sup>

The present study has several strengths and limitations. To our knowledge, this is the first clinical and polysomnographic study that assessed systematically the autonomic symptoms using the validated SCOPA-AUT questionnaire in a large and representative sample of consecutive patients with well-characterized RLS compared to controls. We included a large group of untreated RLS patients to identify clinical, biological and polysomnographic factors associated with autonomic symptoms. However, most of patients had stopped their treatment only 15 days before the study which could affect the report of the autonomic symptoms. Several differences were found between drug naive and drug-free patients for socio-demographic, clinical and polysomnographic data, but not for the SCOPA-AUT score. The proportion of patient with RLS and PLMS index > 15/h was also slightly lower than expected from the literature.<sup>3</sup> Patients with RLS and controls had some clinical and demographic differences; however we took into account a large number of potential confounders and confirmed all our results in a sensitivity analysis including a subgroup of 259 cases and matched controls for age, gender, BMI and CVD. Despite some limitations due to small sample

size, we also provided longitudinal data, with an accurate follow-up of patients evaluated twice in untreated and treated conditions. As another limitation, the SCOPA-AUT questionnaire was initially created for Parkinson's disease, and not for RLS; however this instrument was validated and covers the whole spectrum of problems related to major autonomic areas. No control subjects had a polysomnography assessment, nor ESS, ISI and BDI questionnaires for all controls. Finally, we did not assess for direct measures of the autonomic impairment, nor measures derived from PSG of cardiovascular autonomic control to evaluate and correlate clinical autonomic manifestations with objective measurements of dysautonomia being however out of the scope of this large scale clinical study.

To conclude, in this large case-control study, we found that autonomic symptoms were more common among patients with RLS than controls, in every sub-domains of the SCOPA-AUT questionnaire and even after adjustment for confounding factors especially on depressive symptoms, without key impact of PLMS, sleep fragmentation and RLS medication. This comprehensive assessment for clinical autonomic dysfunction in RLS should be considered systematically, especially in severe patients potentially at risk for CVD.

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**Table 1. Demographic and clinical characteristics of untreated patients with restless legs syndrome (RLS) compared to controls.**

| <i>Variables</i>                                  | <i>Controls</i> |          | <i>RLS</i>      |          | <i>p-value</i> |
|---|-----------------|----------|-----------------|----------|----------------|
|   | <i>n</i>        | <i>%</i> | <i>n</i>        | <i>%</i> |                |
| <i>Demographic and clinical characteristics</i>   |                 |          |                 |          |                |
| Gender, women                                     | 161             | 48.64    | 265             | 64.79    | <0.0001        |
| Age (years) <sup>(1)</sup>                        | 58.98 (± 17.03) |          | 54.13 (± 14.48) |          | <0.0001        |
| BMI (kg/m <sup>2</sup> ) <sup>(1)</sup>           | 24.38 (± 3.44)  |          | 25.68 (± 5.16)  |          | 0.0001         |
| BMI (kg/m <sup>2</sup> )                          |                 |          |                 |          |                |
| <25   | 201             | 60.73    | 215             | 52.57    | <0.0001        |
| [25 ;30[  | 110             | 33.23    | 122             | 29.83    |                |
| ≥30   | 20              | 6.04     | 72              | 17.60    |                |
| <i>Metabolic and cardiovascular comorbidities</i> |                 |          |                 |          |                |
| Hypercholesterolemia, yes                         | 50              | 15.29    | 51              | 12.59    | 0.29           |
| Diabetes type 2, yes                              | 19              | 5.76     | 22              | 5.39     | 0.83           |
| Hypertension, yes                                 | 72              | 21.88    | 77              | 19.01    | 0.34           |
| CVD <sup>(2)</sup> , yes                          | 23              | 6.95     | 54              | 13.40    | 0.005          |

<sup>(1)</sup> Continuous variables are expressed as means (± standard deviation)

<sup>(2)</sup> CVD: coronary artery disease, chronic heart failure, arrhythmia and stroke

**Abbreviations:** BMI = Body Mass Index, CVD = cardiovascular diseases

**Table 2. SCOPA-AUT Total Scores and Subdomain Scores in untreated patients with restless legs syndrome (RLS) compared to controls.**

| Variables                                   | Controls<br>n = 331 |       | RLS<br>n = 409 |       | Model 0           |         | Model 1           |         |
|---|---------------------|-------|----------------|-------|-------------------|---------|-------------------|---------|
|   | n                   | %     | n              | %     | OR [95% CI]       | p-value | OR [95% CI]       | p-value |
| <b>SCOPA-AUT Total Score</b>                |                     |       |                |       |                   |         |                   |         |
| <b>SCOPA-AUT Total Score<sup>(1)</sup></b>  | 8.26 (± 5.80)       |       | 16.53 (± 8.58) |       | 1.19 [1.15;1.22]  | <0.0001 | 1.19 [1.16;1.23]  | <0.0001 |
| <b>SCOPA-AUT Total Score<sup>(2)</sup></b>  |                     |       |                |       |                   |         |                   |         |
| <8  | 178                 | 53.78 | 47             | 11.49 | 1                 | <0.0001 | 1                 | <0.0001 |
| [7 ;16[                                     | 108                 | 32.63 | 159            | 38.88 | 5.58 [3.72;8.35]  |         | 6.57 [4.23;10.2]  |         |
| ≥16   | 45                  | 13.60 | 203            | 49.63 | 17.08 [10.8;26.9] |         | 17.32 [10.6;28.3] |         |
| <b>SCOPA-AUT Subdomain Scores</b>           |                     |       |                |       |                   |         |                   |         |
| <b>SCOPA gastrointestinal<sup>(1)</sup></b> | 1.53 (± 1.84)       |       | 3.63 (± 3.00)  |       | 1.46 [1.35;1.58]  | <0.0001 | 1.44 [1.33;1.56]  | <0.0001 |
| SCOPA gastrointestinal ≥ 1                  | 197                 | 59.52 | 353            | 86.31 | 4.29 [3.00;6.13]  | <0.0001 | 4.18 [2.87;6.10]  | <0.0001 |
| <b>SCOPA urinary<sup>(1)</sup></b>          | 3.39 (± 2.85)       |       | 5.44 (± 3.47)  |       | 1.24 [1.17;1.31]  | <0.0001 | 1.27 [1.19;1.34]  | <.0001  |
| SCOPA urinary ≥ 1                           | 282                 | 85.20 | 392            | 95.84 | 4.01 [2.26;7.10]  | <0.0001 | 5.27 [2.86;9.72]  | <0.0001 |
| <b>SCOPA cardiovascular<sup>(1)</sup></b>   | 0.32 (± 0.70)       |       | 1.14 (± 1.49)  |       | 2.19 [1.80;2.66]  | <0.0001 | 2.09 [1.71;2.56]  | <.0001  |
| SCOPA cardiovascular ≥ 1                    | 74                  | 22.36 | 224            | 54.77 | 4.21 [3.04;5.81]  | <0.0001 | 3.81 [2.71;5.34]  | <0.0001 |
| <b>SCOPA thermoregulatory<sup>(1)</sup></b> | 1.59 (± 1.74)       |       | 3.73 (± 2.54)  |       | 1.60 [1.47;1.75]  | <0.0001 | 1.55 [1.41;1.69]  | <.0001  |
| SCOPA thermoregulatory ≥ 1                  | 208                 | 62.84 | 370            | 90.46 | 5.61 [3.77;8.35]  | <0.0001 | 5.20 [3.41;7.94]  | <0.0001 |
| <b>SCOPA pupillomotor<sup>(1)</sup></b>     | 0.61 (± 0.79)       |       | 1.18 (± 1.04)  |       | 1.97 [1.65;2.34]  | <0.0001 | 1.83 [1.52;2.20]  | <.0001  |
| SCOPA pupillomotor ≥ 1                      | 152                 | 45.92 | 285            | 69.68 | 2.71 [2.00;3.66]  | <0.0001 | 2.46 [1.79;3.38]  | <0.0001 |
| <b>SCOPA sexual in men<sup>(1)</sup></b>    | 1.05 (± 1.58)       |       | 1.06 (± 1.57)  |       | 1.00 [0.86;1.17]  | 0.97    | 1.02 [0.86;1.22]  | 0.81    |
| SCOPA sexual in men ≥ 1                     | 57                  | 43.18 | 58             | 43.61 | 1.02 [0.63;1.65]  | 0.94    | 1.12 [0.64;1.95]  | 0.69    |
| <b>SCOPA sexual in women<sup>(1)</sup></b>  | 1.14 (± 1.47)       |       | 2.20 (± 1.94)  |       | 1.45 [1.24;1.68]  | <0.0001 | 1.50 [1.27;1.78]  | <0.0001 |
| SCOPA sexual in women ≥ 1                   | 62                  | 52.99 | 149            | 75.63 | 2.75 [1.69;4.48]  | <0.0001 | 3.12 [1.84;5.29]  | <.0001  |

<sup>(1)</sup> Continuous variables are expressed as means (± standard deviation)

<sup>(2)</sup> Tertiles of the whole population study (RLS and controls)

Model 0: Crude association, Model 1: Adjustment for age, gender, BMI and cardiovascular disease (except for SCOPA sexual with an adjustment for age, BMI and cardiovascular disease)

**Table 3. Score greater than zero for each item of SCOPA-AUT of untreated patients with restless legs syndrome (RLS) compared to controls.**

| <i>Variables</i>   | <i>Controls</i> |          | <i>RLS</i> |          | <i>Model 0</i>     |                | <i>Model 1</i>     |                |
|--|-----------------|----------|------------|----------|--------------------|----------------|--------------------|----------------|
|  | <i>n</i>        | <i>%</i> | <i>n</i>   | <i>%</i> | <i>OR [95% CI]</i> | <i>p-value</i> | <i>OR [95% CI]</i> | <i>p-value</i> |
| 1. Swallowing/choking                                      | 36              | 10.88    | 125        | 30.56    | 3.61 [2.41;5.41]   | <0.0001        | 3.31 [2.17;5.05]   | <0.0001        |
| 2. Drooling  | 39              | 11.78    | 113        | 27.63    | 2.86 [1.92;4.26]   | <0.0001        | 2.94 [1.93;4.49]   | <0.0001        |
| 3. Dysphagia   | 31              | 9.37     | 101        | 24.69    | 3.17 [2.06;4.89]   | <0.0001        | 2.89 [1.83;4.57]   | <0.0001        |
| 4. Early abdominal fullness                                | 109             | 32.93    | 214        | 52.32    | 2.24 [1.66;3.02]   | <0.0001        | 2.05 [1.49;2.83]   | <0.0001        |
| 5. Constipation  | 75              | 22.66    | 177        | 43.28    | 2.60 [1.88;3.60]   | <0.0001        | 2.47 [1.75;3.50]   | <0.0001        |
| 6. Straining for defecation                                | 110             | 33.23    | 228        | 55.75    | 2.53 [1.87;3.42]   | <0.0001        | 2.49 [1.81;3.44]   | <0.0001        |
| 7. Fecal incontinence                                      | 20              | 6.04     | 48         | 11.74    | 2.07 [1.20;3.56]   | 0.009          | 1.96 [1.10;3.52]   | 0.02           |
| 8. Urinary urgency   | 100             | 30.21    | 174        | 42.54    | 1.71 [1.26;2.32]   | 0.0006         | 1.70 [1.21;2.38]   | 0.002          |
| 9. Urinary incontinence                                    | 71              | 21.45    | 126        | 30.81    | 1.63 [1.17;2.28]   | 0.004          | 1.56 [1.07;2.26]   | 0.02           |
| 10. Incomplete emptying                                    | 115             | 34.74    | 220        | 53.79    | 2.19 [1.62;2.95]   | <0.0001        | 2.30 [1.67;3.18]   | <0.0001        |
| 11. Weak stream of urine                                   | 110             | 33.23    | 179        | 43.77    | 1.56 [1.16;2.11]   | 0.004          | 2.12 [1.50;2.99]   | <0.0001        |
| 12. Pass urine again within two hours of the previous time | 214             | 64.65    | 335        | 81.91    | 2.48 [1.77;3.47]   | <0.0001        | 2.46 [1.72;3.51]   | <0.0001        |
| 13. Nocturia   | 239             | 72.21    | 362        | 88.51    | 2.96 [2.01;4.37]   | <0.0001        | 4.10 [2.65;6.34]   | <0.0001        |
| 14. Lightheaded standing up                                | 50              | 15.11    | 198        | 48.41    | 5.27 [3.69;7.54]   | <0.0001        | 4.82 [3.32;7.01]   | <0.0001        |
| 15. Lightheaded standing for some time                     | 36              | 10.88    | 120        | 29.34    | 3.40 [2.27;5.11]   | <0.0001        | 2.98 [1.94;4.57]   | <0.0001        |
| 16. Syncope  | 11              | 3.32     | 32         | 7.82     | 2.47 [1.22;4.98]   | 0.01           | 2.06 [0.99;4.30]   | 0.05           |
| 17. Hyperhidrosis during the day                           | 60              | 18.13    | 208        | 50.86    | 4.67 [3.33;6.57]   | <0.0001        | 3.86 [2.71;5.50]   | <0.0001        |
| 18. Hyperhidrosis during the night                         | 96              | 29.00    | 243        | 59.41    | 3.58 [2.63;4.88]   | <0.0001        | 3.08 [2.23;4.26]   | <0.0001        |
| 19. Oversensitive to bright light                          | 152             | 45.92    | 285        | 69.68    | 2.71 [2.00;3.66]   | <0.0001        | 2.46 [1.79;3.38]   | <0.0001        |
| 20. Cold intolerance                                       | 147             | 44.41    | 247        | 60.39    | 1.91 [1.42;2.56]   | <0.0001        | 1.96 [1.43;2.68]   | <0.0001        |
| 21. Heat intolerance                                       | 109             | 32.93    | 280        | 68.46    | 4.42 [3.24;6.03]   | <0.0001        | 3.92 [2.82;5.45]   | <0.0001        |
| 22. Erection problem-male                                  | 54              | 39.71    | 39         | 28.68    | 0.61 [0.37;1.01]   | 0.06           | 0.66 [0.37;1.18]   | 0.16           |
| 23. Ejaculation problem-male                               | 41              | 30.83    | 48         | 35.82    | 1.25 [0.75;2.09]   | 0.39           | 1.44 [0.82;2.55]   | 0.21           |
| 24. Vaginal lubrication-female                             | 47              | 38.52    | 115        | 56.65    | 2.09 [1.32;3.30]   | 0.002          | 2.52 [1.52;4.17]   | 0.0003         |
| 25. Problem with orgasm-female                             | 49              | 41.18    | 129        | 64.50    | 2.60 [1.63;4.14]   | <0.0001        | 2.68 [1.64;4.38]   | <0.0001        |

Model 0: Crude association,

Model 1: Adjustment for age, gender (except for item #22 to #24), BMI and cardiovascular disease

**Table 4. Score greater than zero for each item of SCOPA-AUT in drug-naive patients and in drug-free patients with restless legs syndrome (RLS).**

| Variable   | Drug-naive patients<br>N=266 | Drug-free patients*<br>N=143 | p      |
|--|------------------------------|------------------------------|--------|
|  | n (%)                        | n (%)                        |        |
| SCOPA-AUT Total Score <sup>(1)</sup>                       | 16.59 (± 8.11)               | 16.43 (± 9.42)               | 0.44   |
| 1. Swallowing/choking                                      | 84 (31.58)                   | 41 (28.67)                   | 0.54   |
| 2. Drooling  | 71 (26.69)                   | 42 (29.37)                   | 0.56   |
| 3. Dysphagia   | 56 (21.05)                   | 45 (31.47)                   | 0.02   |
| 4. Early abdominal fullness                                | 139 (52.26)                  | 75 (52.45)                   | 0.97   |
| 5. Constipation  | 121 (45.49)                  | 56 (39.16)                   | 0.22   |
| 6. Straining for defecation                                | 150 (56.39)                  | 78 (54.55)                   | 0.72   |
| 7. Fecal incontinence                                      | 23 (8.65)                    | 25 (17.48)                   | < 0.01 |
| 8. Urinary urgency   | 103 (38.72)                  | 71 (49.65)                   | 0.03   |
| 9. Urinary incontinence                                    | 75 (28.20)                   | 51 (35.66)                   | 0.12   |
| 10. Incomplete emptying                                    | 147 (55.26)                  | 73 (51.05)                   | 0.41   |
| 11. Weak stream of urine                                   | 108 (40.60)                  | 71 (49.65)                   | 0.08   |
| 12. Pass urine again within two hours of the previous time | 218 (81.95)                  | 117 (81.82)                  | 0.97   |
| 13. Nocturia   | 230 (86.47)                  | 132 (92.31)                  | 0.08   |
| 14. Lightheaded standing up                                | 137 (51.50)                  | 61 (42.66)                   | 0.09   |
| 15. Lightheaded standing for some time                     | 78 (29.32)                   | 42 (29.37)                   | 0.99   |
| 16. Syncope  | 23 (8.65)                    | 9 (6.29)                     | 0.40   |
| 17. Hyperhidrosis during the day                           | 132 (49.62)                  | 76 (53.15)                   | 0.50   |
| 18. Hyperhidrosis during the night                         | 155 (58.27)                  | 88 (61.54)                   | 0.52   |
| 19. Oversensitive to bright light                          | 195 (73.31)                  | 90 (62.94)                   | 0.03   |
| 20. Cold intolerance                                       | 161 (60.53)                  | 86 (60.14)                   | 0.94   |
| 21. Heat intolerance                                       | 180 (67.67)                  | 100 (69.93)                  | 0.64   |
| 22. Erection problem-male                                  | 27 (30.68)                   | 12 (25.00)                   | 0.48   |
| 23. Ejaculation problem-male                               | 32 (36.78)                   | 16 (34.04)                   | 0.75   |
| 24. Vagina lubrication-female                              | 78 (56.12)                   | 37 (57.81)                   | 0.82   |
| 25. Problem with orgasm-female                             | 89 (64.49)                   | 40 (64.52)                   | 0.99   |

(1) Continuous variables are expressed as mean ( $\pm$  standard deviation)

\*patients who stopped drugs known to alleviate or worsen RLS for at least two weeks before study inclusion



**Table 5. Demographic, clinical and polysomnographic characteristics in drug-naive patients and drug-free patients with restless legs syndrome (RLS).**

| variable                                   | Drug-naive patients | Drug-free patients* | p       |
|--|---------------------|---------------------|---------|
|  | N=266               | N=143               |         |
|  | n (%)               | n (%)               |         |
| Gender, women                              | 175 (65.79)         | 90 (62.94)          | 0.56    |
| Age (years) <sup>(1)</sup>                 | 50.67 (± 14.20)     | 60.57 (± 12.73)     | <0.0001 |
| BMI (kg/m <sup>2</sup> ) <sup>(1)</sup>    | 25.25 (± 5.16)      | 26.49 (± 5.08)      | 0.02    |
| Age at RLS symptom onset <sup>(1)</sup>    | 36.28 (± 16.49)     | 41.98 (± 15.58)     | 0.001   |
| Duration of disease (years) <sup>(1)</sup> | 14.51 (± 11.87)     | 18.72 (± 14.39)     | 0.002   |
| RLS family history, yes                    | 90 (36.73)          | 62 (45.26)          | 0.10    |
| RLS severity scale <sup>(1)</sup>          | 24.29 (± 5.75)      | 29.85 (± 5.55)      | <0.0001 |
| RLS severity scale                         |                     |                     | <0.0001 |
| [11;21[                                    | 84 (31.58)          | 10 (6.99)           |         |
| [21;31[                                    | 137 (51.50)         | 60 (41.96)          |         |
| ≥31  | 45 (16.92)          | 73 (51.05)          |         |
| CVD, yes                                   | 35 (13.31)          | 19 (13.57)          | 0.94    |
| Hypertension, yes                          | 37 (14.07)          | 40 (28.17)          | 0.0007  |
| Diabetes type 2, yes                       | 10 (3.76)           | 12 (8.45)           | 0.05    |
| Hypercholesterolemia, yes                  | 28 (10.61)          | 23 (16.31)          | 0.10    |
| ESS score <sup>(1)</sup>                   | 11.09 (± 5.49)      | 11.79 (± 5.50)      | 0.22    |
| ESS score, >10                             | 145 (54.72)         | 81 (57.45)          | 0.60    |
| BDI score <sup>(1)</sup>                   | 16.91 (± 9.95)      | 16.21 (± 10.09)     | 0.50    |
| BDI score                                  |                     |                     | 0.87    |
| <14  | 111 (42.21)         | 63 (44.68)          |         |
| [14 ;20[                                   | 64 (24.33)          | 34 (24.11)          |         |
| ≥20  | 88 (33.46)          | 44 (31.21)          |         |
| ISI score <sup>(1)</sup>                   | 18.02 (± 4.60)      | 19.36 (± 4.83)      | 0.007   |
| ISI score, >14                             | 211 (79.92)         | 122 (85.31)         | 0.18    |
| Total sleep time (minutes) <sup>(1)</sup>  | 353.69 (± 81.54)    | 296.10 (± 113.72)   | <0.0001 |

|  | Drug-naïve patients<br>N=266 | Drug-free patients*<br>N=143 |         |
|--|------------------------------|------------------------------|---------|
| Sleep efficiency (%) <sup>(1)</sup>                    | 73.62 (± 15.66)              | 62.43 (± 22.36)              | <0.0001 |
| Wake time after sleep onset (minutes) <sup>(1)</sup>   | 85.52 (± 60.22)              | 128.15 (± 81.86)             | <0.0001 |
| Sleep latency (minutes) <sup>(1)</sup>                 | 31.83 (± 35.00)              | 32.86 (± 49.96)              | 0.81    |
| REM sleep latency (minutes) <sup>(1)</sup>             | 116.10 (± 74.11)             | 132.79 (± 90.65)             | 0.06    |
| N1 (%) <sup>(1)</sup>                                  | 7.83 (± 5.98)                | 11.07 (± 12.20)              | 0.002   |
| N2 (%) <sup>(1)</sup>                                  | 53.43 (± 9.94)               | 55.44 (± 14.46)              | 0.11    |
| N3 (%) <sup>(1)</sup>                                  | 19.42 (± 8.43)               | 15.91 (± 10.56)              | 0.0005  |
| REM sleep (%) <sup>(1)</sup>                           | 19.30 (± 7.83)               | 17.81 (± 8.91)               | 0.09    |
| Microarousal index <sup>(1)</sup>                      | 18.77 (± 14.31)              | 42.39 (± 41.08)              | <0.0001 |
| PLMS index (hour) <sup>(1)</sup>                       | 22.79 (± 29.64)              | 70.99 (± 66.07)              | <0.0001 |
| PLMS index (hour), ≥ 15                                | 118 (47.01)                  | 105 (74.47)                  | <0.0001 |
| PLMW index (hour) <sup>(1)</sup>                       | 27.86 (± 27.31)              | 47.68 (± 41.32)              | <0.0001 |
| PLMA index (hour) <sup>(1)</sup>                       | 5.85 (± 10.09)               | 29.50 (± 40.29)              | <0.0001 |
| IAH  | 10.56 (± 14.85)              | 13.30 (± 17.26)              | 0.10    |
| AHI (hour), ≥ 15                                       | 55 (21.91)                   | 41 (29.08)                   | 0.11    |
| SaO <sub>2</sub> <sup>(1)</sup>                        | 95.14 (± 1.76)               | 94.69 (± 3.10)               | 0.09    |
| SaO <sub>2</sub> less than 90% duration <sup>(1)</sup> | 4.21 (± 26.87)               | 4.75 (± 27.19)               | 0.85    |
| Ferritine (µg/L) <sup>(1)</sup>                        | 144.33 (± 116.69)            | 177.20 (± 115.69)            | 0.01    |
| Ferritine (µg/L), ≤50                                  | 49 (20.42)                   | 12 (8.76)                    | 0.004   |

<sup>(1)</sup> Continuous variables are expressed as mean (± standard deviation)

<sup>(2)</sup> CVD: coronary artery disease, chronic heart failure, arrhythmia and stroke

\*patients who stopped drugs known to alleviate or worsen RLS for at least two weeks before study inclusion

**Abbreviations:** AHI = Apnea Hypopnea Index, BMI = Body Mass Index, BDI = Beck Depression Inventory, ESS = Epworth sleepiness scale, ISI = Insomnia Severity Index, RLS = Restless legs syndrome, PLMS = periodic leg movements during sleep, PLMW= periodic leg movements during wakefulness, PLMA = periodic leg movements associated with arousal, REM sleep = rapid eye movement sleep, SaO<sub>2</sub>= Average oxygen saturation

**Table 6. Determinants of a high total SCOPA-AUT score in untreated patients with restless legs syndrome (RLS).**

| Variables  | SCOPA-AUT Total Score |       |                     |       |                        |                        |
|--|-----------------------|-------|---------------------|-------|------------------------|------------------------|
|  | < 19                  |       | ≥ 19 <sup>(1)</sup> |       | p-value <sup>(3)</sup> | p-value <sup>(4)</sup> |
|  | n                     | %     | n                   | %     |                        |                        |
|  | n = 267               |       | n = 142             |       |                        |                        |
| Gender, women  | 160                   | 59.93 | 105                 | 73.94 | 0.005                  |                        |
| Age (years) <sup>(2)</sup>                           | 55.00 (± 14.23)       |       | 52.51 (± 14.87)     |       | 0.10                   |                        |
| BMI (kg/m <sup>2</sup> ) <sup>(2)</sup>              | 25.33 (± 4.70)        |       | 26.35 (± 5.88)      |       | 0.06                   | 0.03                   |
| Age at RLS symptom onset <sup>(2)</sup>              | 39.22 (± 16.27)       |       | 36.67 (± 16.52)     |       | 0.14                   |                        |
| Duration of disease (years) <sup>(2)</sup>           | 16.04 (± 13.10)       |       | 15.99 (± 12.78)     |       | 0.97                   |                        |
| RLS family history, yes                              | 100                   | 39.84 | 52                  | 39.69 | 0.98                   | 0.83                   |
| RLS severity scale <sup>(2)</sup>                    | 25.39 (± 5.95)        |       | 27.82 (± 6.56)      |       | 0.0002                 | 0.0001                 |
| RLS severity scale                                   |                       |       |                     |       |                        |                        |
| [11;21[  | 66                    | 24.72 | 28                  | 19.72 | <0.0001                | <0.0001                |
| [21;31[  | 144                   | 53.93 | 53                  | 37.32 |                        |                        |
| ≥31  | 57                    | 21.35 | 61                  | 42.96 |                        |                        |
| Cardiac disorders, yes                               | 26                    | 9.81  | 28                  | 20.29 | 0.004                  | 0.0006                 |
| Hypertension, yes                                    | 47                    | 17.60 | 30                  | 21.74 | 0.32                   | 0.12                   |
| Diabetes type 2, yes                                 | 7                     | 2.62  | 15                  | 10.64 | 0.002                  | 0.0003                 |
| Hypercholesterolemia, yes                            | 32                    | 12.08 | 19                  | 13.57 | 0.67                   | 0.42                   |
| ESS score <sup>(2)</sup>                             | 10.58 (± 5.44)        |       | 12.80 (± 5.33)      |       | 0.0001                 | 0.0001                 |
| ESS score, >10                                       | 136                   | 50.94 | 90                  | 64.75 | 0.008                  | 0.01                   |
| ISI score <sup>(2)</sup>                             | 17.83 (± 4.64)        |       | 19.74 (± 4.63)      |       | 0.0001                 | 0.0001                 |
| ISI score, >14                                       | 207                   | 77.82 | 126                 | 89.36 | 0.005                  | 0.0007                 |
| BDI score <sup>(2)</sup>                             | 13.66 (± 8.19)        |       | 22.39 (± 10.63)     |       | <0.0001                | <0.0001                |
| BDI score  |                       |       |                     |       | <0.0001                | <0.0001                |
| <14  | 141                   | 53.21 | 33                  | 23.74 |                        |                        |
| [14 ;20[   | 70                    | 26.42 | 28                  | 20.14 |                        |                        |
| ≥20  | 54                    | 20.38 | 78                  | 56.12 |                        |                        |
| Total sleep time (minutes) <sup>(2)</sup>            | 331.61 (± 97.50)      |       | 335.71 (± 99.77)    |       | 0.69                   | 0.74                   |
| Sleep efficiency (%) <sup>(2)</sup>                  | 69.53 (± 19.23)       |       | 69.75 (± 18.90)     |       | 0.91                   | 0.48                   |
| Wake time after sleep onset (minutes) <sup>(2)</sup> | 106.59 (± 75.15)      |       | 89.89 (± 63.36)     |       | 0.03                   | 0.15                   |
| Sleep latency (minutes) <sup>(2)</sup>               | 28.10 (± 39.76)       |       | 39.95 (± 42.14)     |       | 0.009                  | 0.02                   |
| REM sleep latency (minutes) <sup>(2)</sup>           | 125.80 (± 85.69)      |       | 114.55 (± 69.42)    |       | 0.20                   | 0.23                   |
| N1 (%) <sup>(2)</sup>                                | 8.82 (± 7.91)         |       | 9.32 (± 10.45)      |       | 0.60                   | 0.22                   |
| N2 (%) <sup>(2)</sup>                                | 54.31 (± 11.48)       |       | 53.83 (± 12.38)     |       | 0.70                   | 0.85                   |
| N3 (%) <sup>(2)</sup>                                | 18.36 (± 9.05)        |       | 17.79 (± 10.03)     |       | 0.57                   | 0.12                   |

| Variables  | SCOPA-AUT Total Score |            |                     |            |                        |                        |
|--|-----------------------|------------|---------------------|------------|------------------------|------------------------|
|  | < 19                  |            | ≥ 19 <sup>(1)</sup> |            | p-value <sup>(3)</sup> | p-value <sup>(4)</sup> |
|  | n                     | %          | n                   | %          |                        |                        |
| REM sleep (%) <sup>(2)</sup>                           | 18.49                 | (± 7.73)   | 19.29               | (± 9.16)   | 0.36                   | 0.66                   |
| Microarousal index <sup>(2)</sup>                      | 27.92                 | (± 28.42)  | 26.02               | (± 31.22)  | 0.54                   | 0.88                   |
| PLMS index (hour) <sup>(2)</sup>                       | 42.94                 | (± 51.62)  | 34.83               | (± 51.29)  | 0.14                   | 0.78                   |
| PLMS index (hour), ≥ 15                                | 153                   | 59.77      | 70                  | 51.47      | 0.12                   | 0.56                   |
| PLMW index (hour) <sup>(2)</sup>                       | 35.84                 | (± 33.66)  | 33.38               | (± 35.64)  | 0.50                   | 0.89                   |
| PLMA index (hour) <sup>(2)</sup>                       | 15.28                 | (± 26.72)  | 12.62               | (± 29.87)  | 0.37                   | 0.85                   |
| AHI (hour) <sup>(2)</sup>                              | 11.63                 | (± 15.96)  | 11.38               | (± 15.53)  | 0.88                   | 0.53                   |
| AHI (hour), ≥ 15                                       | 62                    | 24.12      | 34                  | 25.19      | 0.82                   | 0.30                   |
| SaO <sub>2</sub> <sup>(2)</sup>                        | 94.89                 | (± 2.55)   | 95.14               | (± 1.87)   | 0.33                   | 0.88                   |
| SaO <sub>2</sub> less than 90% duration <sup>(2)</sup> | 5.08                  | (± 32.14)  | 3.11                | (± 11.74)  | 0.50                   | 0.68                   |
| Ferritine (µg/L) <sup>(2)</sup>                        | 164.52                | (± 119.40) | 140.79              | (± 111.92) | 0.06                   | 0.46                   |
| Ferritine (µg/L), ≤50                                  | 34                    | 13.82      | 27                  | 20.61      | 0.09                   | 0.49                   |

<sup>(1)</sup> Highest tertile of SCOPA-AUT total score in RLS group

<sup>(2)</sup> Continuous variables are expressed as mean (± standard deviation)

<sup>(3)</sup> Crude association

<sup>(4)</sup> Adjustment for gender and age

**Abbreviations:** AHI = Apnea Hypopnea Index, BMI = Body Mass Index, BDI = Beck Depression Inventory, ESS = Epworth sleepiness scale, ISI = Insomnia Severity Index, RLS = Restless legs syndrome, PLMS = periodic leg movements during sleep, PLMW= periodic leg movements during wakefulness, PLMA = periodic leg movements associated with arousal, REM sleep = rapid eye movement sleep, SaO<sub>2</sub>= Average oxygen saturation

**Table 7. Determinants of a high SCOPA-cardiovascular score in untreated patients with restless legs syndrome (RLS).**

| Variables  | SCOPA-cardiovascular Score |       |                    |       | p-value <sup>(3)</sup> | p-value <sup>(4)</sup> |
|--|----------------------------|-------|--------------------|-------|------------------------|------------------------|
|  | <2                         |       | ≥ 2 <sup>(1)</sup> |       |                        |                        |
|  | n                          | %     | n                  | %     |                        |                        |
|  | n = 291                    |       | n = 118            |       |                        |                        |
| Gender, women  | 182                        | 62.54 | 83                 | 70.34 | 0.14                   | 0.11                   |
| Age (years) <sup>(2)</sup>                           | 55.42 (± 13.63)            |       | 50.97 (± 16.02)    |       | 0.005                  |                        |
| BMI (kg/m <sup>2</sup> ) <sup>(2)</sup>              | 25.80 (± 5.17)             |       | 25.39 (± 5.13)     |       | 0.46                   | 0.63                   |
| Age at RLS symptom onset (years) <sup>(2)</sup>      | 39.88 (± 16.17)            |       | 34.60 (± 16.36)    |       | 0.004                  |                        |
| Duration of disease (years) <sup>(2)</sup>           | 15.83 (± 12.58)            |       | 16.49 (± 13.93)    |       | 0.64                   |                        |
| RLS family history, yes                              | 107                        | 39.34 | 45                 | 40.91 | 0.78                   | 0.77                   |
| RLS severity scale <sup>(2)</sup>                    | 25.73 (± 6.07)             |       | 27.49 (± 6.58)     |       | 0.01                   | 0.005                  |
| RLS severity scale                                   |                            |       |                    |       | 0.03                   | 0.02                   |
| [11;21[  | 70                         | 24.05 | 24                 | 20.34 |                        |                        |
| [21;31[  | 148                        | 50.86 | 49                 | 41.53 |                        |                        |
| ≥31  | 73                         | 25.09 | 45                 | 38.14 |                        |                        |
| Cardiac disorders, yes                               | 31                         | 10.76 | 23                 | 20.00 | 0.02                   | 0.006                  |
| Hypertension, yes                                    | 55                         | 18.90 | 22                 | 19.30 | 0.93                   | 0.29                   |
| Diabetes type 2, yes                                 | 16                         | 5.50  | 6                  | 5.13  | 0.88                   | 0.96                   |
| Hypercholesterolemia, yes                            | 39                         | 13.49 | 12                 | 10.34 | 0.39                   | 0.81                   |
| ESS score <sup>(2)</sup>                             | 10.76 (± 5.37)             |       | 12.75 (± 5.58)     |       | 0.001                  | 0.003                  |
| ESS score, >10                                       | 150                        | 51.90 | 76                 | 64.96 | 0.02                   | 0.04                   |
| ISI score <sup>(2)</sup>                             | 18.15 (± 4.76)             |       | 19.33 (± 4.53)     |       | 0.02                   | 0.03                   |
| ISI score, >14                                       | 229                        | 79.24 | 104                | 88.14 | 0.04                   | 0.04                   |
| BDI score <sup>(2)</sup>                             | 14.81 (± 9.23)             |       | 21.22 (± 10.37)    |       | <0.0001                | <0.0001                |
| BDI score  |                            |       |                    |       |                        |                        |
| <14  | 143                        | 49.83 | 31                 | 26.50 | <0.0001                | <0.0001                |
| [14 ;20[   | 74                         | 25.78 | 24                 | 20.51 |                        |                        |
| ≥20  | 70                         | 24.39 | 62                 | 52.99 |                        |                        |
| Total sleep time (minutes) <sup>(2)</sup>            | 332.81 (± 100.18)          |       | 333.58 (± 93.31)   |       | 0.94                   | 0.44                   |
| Sleep efficiency (%) <sup>(2)</sup>                  | 69.18 (± 19.56)            |       | 70.71 (± 17.87)    |       | 0.48                   | 0.88                   |
| Wake time after sleep onset (minutes) <sup>(2)</sup> | 106.35 (± 73.57)           |       | 86.56 (± 64.63)    |       | 0.01                   | 0.11                   |
| Sleep latency (minutes) <sup>(2)</sup>               | 30.56 (± 38.96)            |       | 36.42 (± 45.56)    |       | 0.21                   | 0.24                   |
| REM sleep latency (minutes) <sup>(2)</sup>           | 123.08 (± 84.14)           |       | 118.94 (± 70.81)   |       | 0.65                   | 0.92                   |
| N1 (%) <sup>(2)</sup>                                | 9.31 (± 8.98)              |       | 8.17 (± 8.53)      |       | 0.26                   | 0.55                   |
| N2 (%) <sup>(2)</sup>                                | 54.34 (± 11.85)            |       | 53.65 (± 11.66)    |       | 0.60                   | 0.70                   |

| Variables                                  | SCOPA-cardiovascular Score |       |                    |       | p-value <sup>(3)</sup> | p-value <sup>(4)</sup> |
|--|----------------------------|-------|--------------------|-------|------------------------|------------------------|
|  | <2                         |       | ≥ 2 <sup>(1)</sup> |       |                        |                        |
|  | n                          | %     | n                  | %     |                        |                        |
| N3 (%) <sup>(2)</sup>                      | 18.08 (± 9.52)             |       | 18.38 (± 9.08)     |       | 0.78                   | 0.89                   |
| REM sleep (%) <sup>(2)</sup>               | 18.38 (± 7.79)             |       | 19.77 (± 9.28)     |       | 0.13                   | 0.24                   |
| Microarousal index <sup>(2)</sup>          | 27.40 (± 29.54)            |       | 26.92 (± 29.13)    |       | 0.88                   | 0.47                   |
| PLMS index (hour) <sup>(2)</sup>           | 39.85 (± 49.53)            |       | 40.84 (± 56.75)    |       | 0.86                   | 0.18                   |
| PLMS index (hour), ≥ 15                    | 161                        | 57.09 | 62                 | 56.36 | 0.90                   | 0.41                   |
| PLMW index (hour) <sup>(2)</sup>           | 35.65 (± 34.24)            |       | 33.27 (± 34.68)    |       | 0.54                   | 0.97                   |
| PLMA index (hour) <sup>(2)</sup>           | 14.25 (± 27.61)            |       | 14.63 (± 28.56)    |       | 0.90                   | 0.30                   |
| Apnea-hypopnea index (hour) <sup>(2)</sup> | 12.29 (± 16.67)            |       | 9.63 (± 13.16)     |       | 0.14                   | 0.35                   |
| Apnea-hypopnea index (hour), ≥ 15          | 74                         | 26.24 | 22                 | 20.00 | 0.20                   | 0.48                   |
| SaO2 <sup>(2)</sup>                        | 94.90 (± 2.58)             |       | 95.19 (± 1.57)     |       | 0.26                   | 0.70                   |
| SaO2 less than 90% duration <sup>(2)</sup> | 3.01 (± 12.11)             |       | 8.03 (± 47.25)     |       | 0.16                   | 0.10                   |
| Ferritine (µg/L) <sup>(2)</sup>            | 165.74 (± 121.91)          |       | 134.17 (± 102.69)  |       | 0.02                   | 0.05                   |
| Ferritine (µg/L), ≤50                      | 40                         | 15.15 | 21                 | 18.58 | 0.41                   | 0.93                   |

<sup>(1)</sup> Highest tertile of SCOPA-AUT total score in RLS group

<sup>(2)</sup> Continuous variables are expressed as mean (± standard deviation)

<sup>(3)</sup> Crude association

<sup>(4)</sup> Adjustment for age

**Abbreviations:** AHI = Apnea Hypopnea Index, BMI = Body Mass Index, BDI = Beck Depression Inventory, ESS = Epworth sleepiness scale, ISI = Insomnia Severity Index, RLS = Restless legs syndrome, PLMS = periodic leg movements during sleep, PLMW= periodic leg movements during wakefulness, PLMA = periodic leg movements associated with arousal, REM sleep = rapid eye movement sleep, SaO2= Average oxygen saturation