**Supplemental Data**

**Methods**

***Questionnaires***

**Insomnia Severity Index**. Insomnia Severity Index (ISI), a 7-item self-report questionnaire, was used for assessing the nature, severity, and impact of insomnia [1]. It is a brief, reliable, and valid instrument that was designed to assess the severity of both night-time and daytime components of insomnia, and widely used to screening for insomnia and evaluating treatment outcome [1,2]. The usual recall period is the “last month” and the dimensions evaluated are: (i) severity of sleep onset, (ii) sleep maintenance, and (iii) early morning awakening problems, (iv) sleep dissatisfaction, (v) interference of sleep difficulties with daytime functioning, (vi) noticeability of sleep problems by others, and (vii) distress caused by the sleep difficulties. Content of the ISI corresponds in part to the DSM-IV diagnostic criteria for insomnia [3]. A 5-point Likert scale is used to rate each item (e.g., 0 = no problem; 4 = very severe problem), yielding a total score ranging from 0 to 28. The total score is interpreted as follows: absence of insomnia (0-7); sub-threshold insomnia (8-14); moderate insomnia (15-21); and severe insomnia (22-28). A cut-off score lower than eight is likely to yield too many false positives, whereas one above 14 would be too stringent and produce too many false negatives [2].

**STOP-Bang**. The Snoring, Tiredness, Observed apnoea, high blood Pressure (STOP)-BMI, age, neck circumference and gender (Bang) questionnaire was developed in response to the need for a concise, user-friendly OSA screening tool in preoperative clinics [4] and includes the four questions related to the clinical features of sleep apnoea (snoring, tiredness, observed apnoea, and high blood pressure - BP) *plus* four additional demographic queries, for a total of eight dichotomous. For each question, answering “yes” scores 1, a “no” response scores 0, and the total score ranges from 0 to 8 [4]. It can be completed quickly and easily (usually within 1-2 minutes), and overall response rates are typically high (90% - 100%) [4,5]. The probability of moderate-to-severe OSA increases in direct proportion to the STOP-Bang score, which makes the questionnaire an easily used tool for identifying patients at high risk for OSA.

**Restless Legs Syndrome Rating Scale**. The risk of RLS was assessed using the RLS Rating Scale [6]. This scale, validated in 2003 by the International Restless Legs Syndrome Study Group (IRLSS), meets performance criteria for a brief, patient completed instrument that can be used to assess RLS severity for purposes of clinical assessment, research, or therapeutic trials, supporting the finding that RLS is a relatively uniform disorder in which the severity of the basic symptoms is strongly related to their impact on the patient’s life [6]. It consists of ten questions, which can be divided in four mains group: (i) primary measures of symptom severity (questions 1, 2, and 6) (ii) and intensity/frequency (questions 7 and 8), (iii) impact on sleep (questions 4 and 5), and (iv) impact on mood and daily functions (questions 9 and 10) [6]. Each question had a set of five response options graded from no RLS or impact (score = 0) to very severe RLS or impact (score = 4); this produced a total scale whose overall score could range from 0 to 40. Only a score of 0 can be retained as an absence of disease.

**Epworth Sleepiness Scale**. The ESS is based on the chances of dozing off in eight imaginary situations. A subject who scores ≥ 10 or above is at high risk of excessive daytime sleepiness (EDS). Its use in clinical practice derived from the capacity to estimate the EDS caused by short sleep duration and poor sleep quality. Even though the ESS remains an instrument recommended by the most recent guidelines for OSA screening [7], recently it has been confirmed that it is less accurate and it has lower diagnostic odds ratio, sensitivity and specificity, comparing with other questionnaire, such as the STOP-Bang and the Berlin Questionnaire [8,9], especially for mild-to-moderate OSA screening and for predicting its severity.

***Echocardiography***

M-mode and 2D echocardiography was performed with a 3.5-MHz transducer. Measurements were performed by averaging at least 3 cardiac cycles according to the European and American Society of Echocardiography guidelines [10,11]. Left ventricular (LV) mass was calculated from end-diastolic measurements using Devereux’s formula and normalized by height (in meters) to the 2.7 power (LVMI) [11]; left ventricular hypertrophy (LVH) was defined when LVMI was LVM/height ≥ 48 g/m2.7 for men and ≥ 44 g/m2.7 for women following current recommendations [12]. LV filling was evaluated from the apical 4-chamber view by recording the mitral flow with pulsed Doppler technique with the sample volume placed at the tips of the mitral leaflets: peak early trans-mitral flow velocity (E), late-diastolic flow velocity (A) and the ratio of the early to late peak (E/A ratio). Tissue Doppler indexes were recorded at a horizontal speed of 100 mm/s: early diastolic peak velocity of septal mitral annulus (e'). The ratio between transmitral E and e' (E/e' ratio) and the left atrial volume index (LAVI) were examined as indexes of altered diastolic LV filling [11].

***Extended statistical analysis***

At the multivariate analysis, to avoid collinearity, we calculated the center-weighted mean score for the RLS Rating Scale and the STOP-Bang, and then subtracted these values from the absolute values of these questionnaires. We, therefore, created a variable (by multiplying these subtracted values) that was used in the regression model. The results of this further regression showed, not only that the STOP-Bang centered remained the strongest predictor of LVMI (p<0.0001), but also that there was an interaction between STOP-Bang and RLS Rating Scale score in determining LVMI (β -0.184, p=0.012). The SPSS Syntax algorithm is showed in Figure 2 and the output of this analysis in Table 1.

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| **Table 1. Multivariate regression including the interaction analysis between RLS Rating Scale and STOP-Bang score.****Model Summary**  |
| Model | R | R Square | Adjusted R Square | Std. Error of the Estimate | Change Statistics |
| R Square Change | F Change | df1 | df2 | Sig. F Change |
| 1 | .468a | .219 | .183 | 9.8942 | .219 | 6.041 | 7 | 151 | .000 |
| 2 | .468b | .219 | .188 | 9.8616 | .000 | .001 | 1 | 151 | .971 |
| 3 | .467c | .218 | .193 | 9.8324 | .000 | .095 | 1 | 152 | .759 |
| 4 | .465d | .217 | .196 | 9.8116 | -.002 | .349 | 1 | 153 | .556 |

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| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
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| **ANOVA a** |
| Model | Sum of Squares | df | Mean Square | F | Sig. |
| 1 | Regression | 4139.888 | 7 | 591.413 | 6.041 | .000b |
| Residual | 14782.059 | 151 | 97.894 |   |   |
| Total | 18921.947 | 158 |   |   |   |
| 2 | Regression | 4139.761 | 6 | 689.960 | 7.095 | .000c |
| Residual | 14782.185 | 152 | 97.251 |   |   |
| Total | 18921.947 | 158 |   |   |   |
| 3 | Regression | 4130.544 | 5 | 826.109 | 8.545 | .000d |
| Residual | 14791.403 | 153 | 96.676 |   |   |
| Total | 18921.947 | 158 |   |   |   |
| 4 | Regression | 4096.833 | 4 | 1024.208 | 10.639 | .000e |
| Residual | 14825.113 | 154 | 96.267 |   |   |
| Total | 18921.947 | 158 |   |   |   |

a. Dependent Variable: left ventricular mass index (LVMI)b. Predictors: (Constant), centered RLS Rating Scale score, PAC, centered STOP-Bang and RLS Rating Scale score, 24-h urinary Na+, Age, Systolic Blood Pressure, centered STOP-Bang c. Predictors: (Constant), centered RLS Rating Scale score, PAC, centered STOP-Bang and RLS Rating Scale score, Age, Systolic Blood Pressure, centered STOP-Bang d. Predictors: (Constant), centered RLS Rating Scale score, centered STOP-Bang and RLS Rating Scale score, Age, Systolic Blood Pressure, centered STOP-Bange. Predictors: (Constant), centered STOP-Bang and RLS Rating Scale score, Age, Systolic Blood Pressure, centered STOP-Bang |

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| **Coefficients a**  |
| Model | Unstandardized Coefficients | Standardized Coefficients | t | Sig. | 95.0% Confidence Interval for B | Correlations | Collinearity Statistics |
| B | Std. Error | Beta | Lower Bound | Upper Bound | Zero-order | Partial | Part | Tolerance | VIF |
| 1 | (Constant) | 27.598 | 8.061 |  | 3.424 | .001 | 11.671 | 43.526 |  |  |  |  |  |
| Age | .157 | .096 | .126 | 1.644 | .102 | -.032 | .346 | .244 | .133 | .118 | .883 | 1.132 |
| Systolic blood pressure | .089 | .049 | .137 | 1.824 | .070 | -.007 | .185 | .214 | .147 | .131 | .914 | 1.094 |
| 24-h urinary Na+ | .000 | .012 | -.003 | -.036 | .971 | -.023 | .023 | .074 | -.003 | -.003 | .923 | 1.084 |
| Plasma aldosterone concentration | .001 | .003 | .023 | .308 | .759 | -.005 | .007 | .030 | .025 | .022 | .951 | 1.051 |
| Centered STOP-Bang and RLS Rating Scale score | -.232 | .092 | -.183 | -2.517 | .013 | -.415 | -.050 | -.240 | -.201 | -.181 | .974 | 1.027 |
| Centered STOP-Bang  | 2.099 | .552 | .296 | 3.801 | .000 | 1.008 | 3.191 | .374 | .295 | .273 | .851 | 1.175 |
| Centered RLS Rating Scale score | .072 | .124 | .042 | .579 | .564 | -.173 | .316 | .081 | .047 | .042 | .983 | 1.017 |
| 2 | (Constant) | 27.543 | 7.888 |  | 3.492 | .001 | 11.959 | 43.128 |  |  |  |  |  |
| Age | .157 | .095 | .126 | 1.659 | .099 | -.030 | .345 | .244 | .133 | .119 | .890 | 1.123 |
| Systolic blood pressure | .089 | .048 | .137 | 1.837 | .068 | -.007 | .184 | .214 | .147 | .132 | .926 | 1.080 |
| Plasma aldosterone concentration | .001 | .003 | .023 | .308 | .759 | -.005 | .007 | .030 | .025 | .022 | .952 | 1.051 |
| Centered STOP-Bang and RLS Rating Scale score | -.233 | .092 | -.184 | -2.533 | .012 | -.414 | -.051 | -.240 | -.201 | -.182 | .978 | 1.022 |
| Centered STOP-Bang  | 2.094 | .534 | .296 | 3.921 | .000 | 1.039 | 3.150 | .374 | .303 | .281 | .904 | 1.106 |
| Centered RLS Rating Scale score | .072 | .123 | .042 | .583 | .561 | -.171 | .315 | .081 | .047 | .042 | .986 | 1.014 |
| 3 | (Constant) | 27.999 | 7.725 |  | 3.624 | .000 | 12.737 | 43.261 |  |  |  |  |  |
| Age | .162 | .094 | .129 | 1.725 | .087 | -.023 | .347 | .244 | .138 | .123 | .909 | 1.101 |
| Systolic blood pressure | .086 | .047 | .133 | 1.816 | .071 | -.008 | .179 | .214 | .145 | .130 | .955 | 1.047 |
| Centered STOP-Bang and RLS Rating Scale score | -.232 | .092 | -.183 | -2.535 | .012 | -.413 | -.051 | -.240 | -.201 | -.181 | .979 | 1.022 |
| Centered STOP-Bang  | 2.100 | .532 | .296 | 3.947 | .000 | 1.049 | 3.152 | .374 | .304 | .282 | .905 | 1.104 |
| Centered RLS Rating Scale score | .072 | .123 | .043 | .591 | .556 | -.170 | .315 | .081 | .048 | .042 | .986 | 1.014 |
| 4 | (Constant) | 27.506 | 7.664 |  | 3.589 | .000 | 12.367 | 42.646 |  |  |  |  |  |
| Age | .165 | .093 | .132 | 1.769 | .079 | -.019 | .349 | .244 | .141 | .126 | .912 | 1.096 |
| Systolic blood pressure | .088 | .047 | .136 | 1.876 | .063 | -.005 | .181 | .214 | .149 | .134 | .962 | 1.040 |
| Centered STOP-Bang and RLS Rating Scale score | -.233 | .091 | -.184 | -2.554 | .012 | -.414 | -.053 | -.240 | -.202 | -.182 | .979 | 1.021 |
| Centered STOP-Bang  | 2.100 | .531 | .296 | 3.954 | .000 | 1.051 | 3.149 | .374 | .304 | .282 | .905 | 1.104 |
| 1. Dependent Variable: left ventricular mass index (LVMI)
 |
| **Collinearity Diagnostics a** |
| Model | Dimension | Eigenvalue | Condition Index | Variance Proportions |
| (Constant) | Age | SBP | 24-h uNa+ | PAC | Centered STOP-Bang and RLS | Centered STOP-Bang | Centered RLS |
| 1 | 1 | 4.440 | 1.000 | .00 | .00 | .00 | .01 | .01 | .00 | .00 | .00 |
| 2 | 1.140 | 1.974 | .00 | .00 | .00 | .00 | .00 | .38 | .34 | .08 |
| 3 | .986 | 2.122 | .00 | .00 | .00 | .00 | .00 | .04 | .05 | .90 |
| 4 | .877 | 2.250 | .00 | .00 | .00 | .00 | .00 | .57 | .47 | .00 |
| 5 | .417 | 3.264 | .00 | .00 | .00 | .02 | .92 | .00 | .00 | .00 |
| 6 | .112 | 6.302 | .00 | .04 | .01 | .89 | .02 | .01 | .03 | .01 |
| 7 | .022 | 14.302 | .05 | .90 | .15 | .08 | .02 | .00 | .07 | .00 |
| 8 | .006 | 27.636 | .94 | .05 | .84 | .01 | .03 | .00 | .04 | .01 |
| 2 | 1 | 3.577 | 1.000 | .00 | .00 | .00 |  | .02 | .00 | .00 | .00 |
| 2 | 1.139 | 1.772 | .00 | .00 | .00 |  | .00 | .39 | .36 | .08 |
| 3 | .985 | 1.906 | .00 | .00 | .00 |  | .00 | .04 | .05 | .90 |
| 4 | .876 | 2.021 | .00 | .00 | .00 |  | .00 | .56 | .51 | .00 |
| 5 | .394 | 3.012 | .00 | .00 | .00 |  | .92 | .00 | .00 | .00 |
| 6 | .023 | 12.428 | .04 | .95 | .12 |  | .02 | .00 | .05 | .00 |
| 7 | .006 | 24.745 | .96 | .04 | .88 |  | .03 | .00 | .03 | .01 |
| 3 | 1 | 2.971 | 1.000 | .00 | .00 | .00 |  |  | .00 | .00 | .00 |
| 2 | 1.139 | 1.615 | .00 | .00 | .00 |  |  | .39 | .36 | .08 |
| 3 | .985 | 1.737 | .00 | .00 | .00 |  |  | .04 | .05 | .90 |
| 4 | .875 | 1.842 | .00 | .00 | .00 |  |  | .57 | .51 | .00 |
| 5 | .024 | 11.235 | .04 | .93 | .13 |  |  | .00 | .05 | .00 |
| 6 | .006 | 22.170 | .96 | .06 | .87 |  |  | .01 | .03 | .01 |
| 4 | 1 | 2.971 | 1.000 | .00 | .00 | .00 |  |  | .00 | .00 |  |
| 2 | 1.124 | 1.626 | .00 | .00 | .00 |  |  | .43 | .41 |  |
| 3 | .876 | 1.842 | .00 | .00 | .00 |  |  | .56 | .51 |  |
| 4 | .024 | 11.226 | .04 | .94 | .13 |  |  | .00 | .05 |  |
| 5 | .006 | 22.051 | .96 | .06 | .87 |  |  | .01 | .03 |  |
| a. Dependent Variable: left ventricular mass index (LVMI) |

SBP, systolic blood pressure; PAC, plasma aldosterone concentration; 24-h uNa+, 24-hours urinary sodium.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **STOP-Bang** | *P* | **ISI** | *P* | **RLS Rating Scale** | *P* |
|  |  **≥ 3****(*n* = 84)** | **< 3****(*n* = 75)** |  | **≥ 8****(*n* = 48)** | **< 8****(*n* = 111)** |  | **≥ 1****(*n* = 89)** | **0****(*n* = 70)** |  |
| **Urinary Epinephrine excretion** (µmol/24h) | 36(31) | 29(38) | ns | 36(24) | 36(27) | ns | 36(27) | 36(23) | ns |
| **Urinary Norepinephrine** **excretion** (µmol/24h) | 375(270)\* | 326(210) | 0.018 | 325(181) | 368(242) | ns | 362(225) | 336(227) | ns |
| **Urinary Metanephrine excretion** (µmol/24h) | 0.15(0.13) | 0.17(0.08) | ns | 0.15(0.15) | 0.18(0.13) | ns | 0.18(0.14) | 0.14(0.57) | ns |
| **Urinary Normetanephrine excretion** (µmol/24h) | 0.30(0.29) | 0.30(0.30) | ns | 0.28(0.27) | 0.34(0.29) | ns | 0.29(0.29) | 0.32(0.29) | ns |

**Table 2. Sympathetic nervous system evaluation by the indirect method of 24-h urinary catecholamines measurement.**

ISI, insomnia severity index; RLS, restless legs syndrome.

Data expressed by median (and interquartile range).

\*p <0.05 *vs* ISI ≥ 8

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **STOP-Bang** | *P* | **ISI** | *P* | **RLS Rating Scale** | *P* |
|  |  **≥ 3****(*n* = 84)** | **< 3****(*n* = 75)** |  | **≥ 8** **(*n* = 48)** | **< 8****(*n* = 111)** |  | **≥ 1** **(*n* = 89)** | **0****(*n* = 70)** |  |
| **STOP-Bang score** | 5 (2)# | 2 (1) | < 0.0001 | 3 (3) | 3 (1) | 0.037 | 3 (2) | 3 (2) | ns |
| **ISI score** | 7 (5) | 6 (7) | ns | 10 (5)\* | 4 (5) | < 0.0001 | 7 (6) | 5 (6) | ns |
| **RLS Rating Scale score** | 4 (6) | 4 (7) | ns | 4 (16) | 3 (5) | 0.028 | 5 (8)§ | - | - |
| **ESS**  | 5 (3) | 5 (4) | ns | 6 (4) | 5 (3) | 0.002 | 5 (4) | 5 (4) | ns |

**Table 3. STOP-Bang, Insomnia Severity Index (ISI), Restless Legs Syndrome (RLS) Rating Scale, and Epworth Sleepiness Scale (ESS) evaluation in the subgroups of patients with and without high risk of obstructive sleep apnoea, insomnia and RLS, based on the relative questionnaire scores.**

Data expressed by median (and interquartile range).

# p <0.0001 *vs* RLS Rating Scale ≥ 1 and ISI ≥ 8

\*p <0.005 *vs* RLS Rating Scale ≥ 1 and STOP-Bang ≥ 3

§p <0.005 *vs* ISI ≥ 8 and STOP-Bang ≥ 3

|  |
| --- |
|  **ISI** *P* **RLS Rating Scale** *P* |
|  | **> 14** **(*n* = 11)** | **≤ 14****(*n* = 148)** |  | **> 10** **(*n* = 26)** | **≤ 10****(*n* = 133)** |  |
| **Serum creatinine** (μmol/l) | 68(33) | 77(19) | ns | 68(20) | 77(18) | ns |
| **eGFR** (mL/min/1.73m2) | 91(20) | 108(20) | 0.003 | 103(21) | 109(20) | ns |
| **UAE** (mg/24h) | 31.2(32.9) | 11.2(20.5) | 0.005 | 26.3(28.1) | 10.8(15.7) | 0.008 |
| **Left ventricular mass index** (g/m2.7) | 49.6(18.6) | 47.7(11.5) | ns | 48.9(15.4) | 47.1(11.1) | ns |
| **Left atrial volume index** (ml/m2) | 25.0(8.0) | 25.7(3.0) | ns | 26.0(4.5) | 27.5(4.0) | 0.03 |
| **Aortic root diameter** (mm) | 33.0(6.0) | 33.6(3.0) | ns | 33.6(5.0) | 33.6(3.0) | ns |

**Table 4. Renal and cardiac markers of hypertension-mediated organ damage in patients with higher risk of insomnia and restless legs syndrome (RLS) compared to the subgroup with lower scores, using cut-off > 14 for Insomnia Severity Index and > 10 for RLS.**

Data expressed by median (and IQR).

eGFR, estimated glomerular filtration rate (CDK-EPI); UAE, 24-h urinary albumin excretion.

**Figure 1. Flow-chart of the study.**

SBP, systolic blood pressure; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; RLS, restless legs syndrome.



**Figure 1. SPSS Syntax algorithm.**

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