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Article

Predictive values of nocturia and its voiding frequency on the Aging Males' Symptoms

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Abstract: Background: The link between nocturia and aging male symptoms (AMS) has not been scientifically established. This study aimed to measure the degree of severity of AMS that impact on the health-related quality-of-life (HRQoL) in adult males living with nocturia, and to determine the predictive values of nocturnal factors on AMS. Methods: It is an extended analysis of new data collected by using the Hong Kong Traditional AMS (HK-AMS) scale and Cantonese version of the Pittsburgh Sleep Quality Index (PSQI) in a recently published cross-sectional population-based survey. Results: Of the 781 respondents that have completed the set of questionnaires, 68% and 61% of men living with nocturia reported clinically significant (at moderate-to-severe levels) somato-vegetative and sexual AMS, whereas the prevalence and severity were increased with advancing nighttime voiding frequency. The nocturia-specific QoL (NQoL) score and nocturnal frequency were found to be significant predictive factors for composite, somato-vegetative and sexual AMS, in addition to age, global OSQI score, and certain metabolic diseases. Conclusions: Current findings suggested the inclusion of nocturia when measuring the male-specific HRQoL related to aging.

Keywords: Nocturia; aging male symptoms, Quality of life; Health-related Quality of life, Male adults, NQoL, Urinary frequency, Bedtime urination, sleep.

1. Introduction

Nocturia caused much public health concerns because of its impact on quality-of-life (QoL), in addition to its associations with numerous illnesses and conditions [1]. Nocturia is often co-morbid with sleep disturbance impacted dominantly life activities and their function levels [2]. Besides, accumulating evidence has linked nocturia with certain health risk. Particularly in elderly, nocturia has been a known risk factor for fall [3]. But recent research conducted in Korea has extended the risk associations of nocturia on slipping and falling to all ages of adult males [4]. In this relation, the Nocturia Quality of life module of the International Consultation on Incontinence Modular Questionnaire (ICIQ-NQoL) has shown to be a useful tool for predicting the risk of falling [5]. Owing to its implication on sleep, nocturia was identified as a stronger predictive symptom than snoring for obstructive sleep apnea, whereas nocturnal frequency was even found to be reflective in the severity of broad sleep-disordered breathing [6-7]. Sleep disturbance caused by nocturia negatively impacted on one's overall well-being, general health, vitality, and essential biological rhythms [8-9].

Our recent research has reported 63% and 80% of Hong Kong adult males were living respectively with nocturia [10] and aging male symptoms (AMS) [11] that both were correlated with age, but also shared strong associations with a bundle of metabolic and urological conditions harming the health-related quality-of-life (HRQoL). All these conditions were link with the decline of testosterone levels in men [12]. Testosterone levels

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decline with age resulting in deterioration of men's health [13-14]. Accumulating evidence supported the benefits of testosterone replacement therapy for treating symptoms of late-onset hypogonadism in improving lower urinary tract symptoms (LUTS) [15] and numerous metabolic conditions such as insulin resistance, adiposity, and dyslipidaemia [16]. Total serum testosterone level was found to be negatively correlated with prostate volume suggesting its relationship with benign prostate hyperplasia (BPH), but also insulin level and array of obesity-related factors that further linked testosterone to metabolic syndrome [16-18]. On the other hand, testosterone was also interplayed between nocturia and sleep. Production of testosterone was interfered when sleep was fragmented to a level failing to show rapid eye movement (REM), as caused by nocturia [19]. Interestingly, latest research indicated the dual roles of testosterone on sleep quality that could be affected by both deprived and excessive supplies in the circulation, whereas obesity was shown to exhibited mediating roles in the inter-correlation between serum testosterone and sleep efficiency [20]. Well-designed sleep restriction experiments have clearly shown the effects of sleep deprivation in testosterone reduction [21], which may also lead to other health impact associated with nocturia and AMS. The ICIQ-NQoL questionnaire consisted of two subscales with one particularly measures the sleep/energy factor [22] while there are two items in the 'Aging male' symptoms (AMS) scale specifically asking about the sleep problem and consequence [23]. Within the context of men's HRQoL, considering testosterone may play a central role in nocturia to form part of the AMS. The objective of this study is to determine the predictive values of nocturia and its related factors on AMS.

2. Materials and Methods

2.1. Study Design

This is an extended study of the community-based survey on nocturia that our research team has conducted recently [10]. It involves the analysis and interpretation of unpublished data set on AMS and sleep quality that was collected among adult males who were reported of suffering from nocturia. In accordance with the street-intercept and random walk design, respondents with nocturia were also invited to complete the AMS scale and the Pittsburgh Sleep Quality Index (PSQI) on site after administering the NQoL questionnaire and collecting the demographic information.

2.2. The Instruments and Measurements

The Hong Kong Traditional AMS (HK-AMS) scale [11] and the Cantonese version of the PSQI (CPSQI) [24] were adopted in this study.

The HK-AMS scale consisted of 17 items using the 5-point Likert scale (from 1 to 5) of "severity" to measure the personal perception of respondents on male symptoms or complaints associated with aging. The scores of relevant items were summed to generate the composite score (ranged 17-85) and 3 domain scores in 3 dimensions: samato-vegetative (ranged 7-35), psychological (ranged 5-25), and sexual (ranged 5-25). Higher score represented a higher severity of the aging symptoms, whereas the composite score can be further categorized into 4 severity levels as 'no significant symptoms' (<26), 'mild' (27-36), 'moderate' (37-49), and 'severe' (>50). Furthermore, the domain scores were categoized into different severity levels according to Heinemann et al. [23]. The psychometric prosperities with similar male population have been reported in Yuen et al. [11].

The 19-item CPSQI is a well-validated questionnaire that has been used for measuring the subjective sleep quality of different Chinese populations [24]. The items are categorized into 7 components scores (each ranged 0-3), which are summed to produce a 0-21 global score ranged and any scores >5 to indicate poor sleeper.

2.3. Data Processing and Statistical Analysis

Data collected from the survey were entered and analyzed using the SPSS version 25.0 (IBM, Armonk, NY, USA) and the Prism version 9.0 (GraphPad, San Diego, CA, YSA). Descriptive statistics were used for reporting the categorical variables (frequency and percentage) and continuous variables (mean and standard deviation (SD)) of the

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demographics, nocturnal frequency, NQoL scores, and AMS and sleep conditions. Significant differences among nominal and continuous variables between groups were evaluated by using Chi-squared (χ^2), students' t-test, and one-way ANOVA accordingly. The Person's correlation analysis was used to access the linear correlations among continuous variables. Furthermore, stepwise multiple regression analysis was performed to determine the multicollinearity among different variables to identify the significant predictive factors for AMS in the studied population.

3. Results

A total of 781 respondents have indicated at least one nocturnal episode per night and completed the extended survey with the HK-AMS and CPSQI. Table 1 has summarized the demographics, heath conditions, NQoL characteristics, AMS and sleep quality. The studied population was reported with the prevalence of 1, 2, 3, and ≥4 voiding episodes per night were 50.4%, 32.5%, 12.3%, and 4.7%, respectively [10].

Table 1. A summary of demographic and health-related characteristics of the studied adult male population living with nocturia.

Variables	Number (Percentage)
Number of respondents	781 (100.0)
Age (years), mean ± SD	60.5 ± 14.0
Age group (years)	
≤40	65 (8.3)
41-50	108 (12.8)
51-60	182 (23.3)
61-70	217 (27.8)
≥71	209 (26.8)
Married or cohabited	533 (68.3)
Current smoker	452 (57.9)
Daily drinker	205 (26.3)
Diseases	
Diabetes mellitus (DM)	147 (18.8)
Hypertension (HTN)	350 (44.8)
DM+HTN comorbidity	123 (15.8)
Prostate cancer	5 (0.6)
Benign Prostate hyperplasia (BPH)	87 (11.1)
On BPH medication	58 (7.4)
Nocturia	
Mean overall NQoL score, mean ± SD	14.1 ± 9.1
Mean sleep/energy factor score, mean ± SD	6.0 ± 4.8
Mean bother/concern factor score, mean ± SD	7.7 ± 5.4
Poor or very poor NQoL	116, 14.9
AMS	
Mean composite score, mean ± SD	31.6 ± 8.4
Mean somato-vegetative score, mean ± SD	14.9 ± 4.3
Mean psychological score, mean ± SD	7.5 ± 2.7
Mean sexual score, mean ± SD	9.2 ± 3.6
Sleep quality	
Mean global PSQI score, mean ± SD	6.7 ± 3.3
Poor sleeper (Global PSQI score >5)	389 (49.8)

3.1. High prevalence of somato-vegeative and sexual AMS among adult males living with nocturia

The studied male population was not only living with nocturia but also at mild level of total AMS with a mean composite score of 31.6 ± 8.4, moderate level of somato-vegetative symptoms at mean score of 14.9 ± 4.3, and moderate-to-severe level of sexual

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symptoms at mean score of 9.2 ± 3.6 (Table 1). In addition, almost half of the nocturnal population was being rated as poor sleeper with a mean PSQI score of 6.7 ± 3.3 (Table 1).

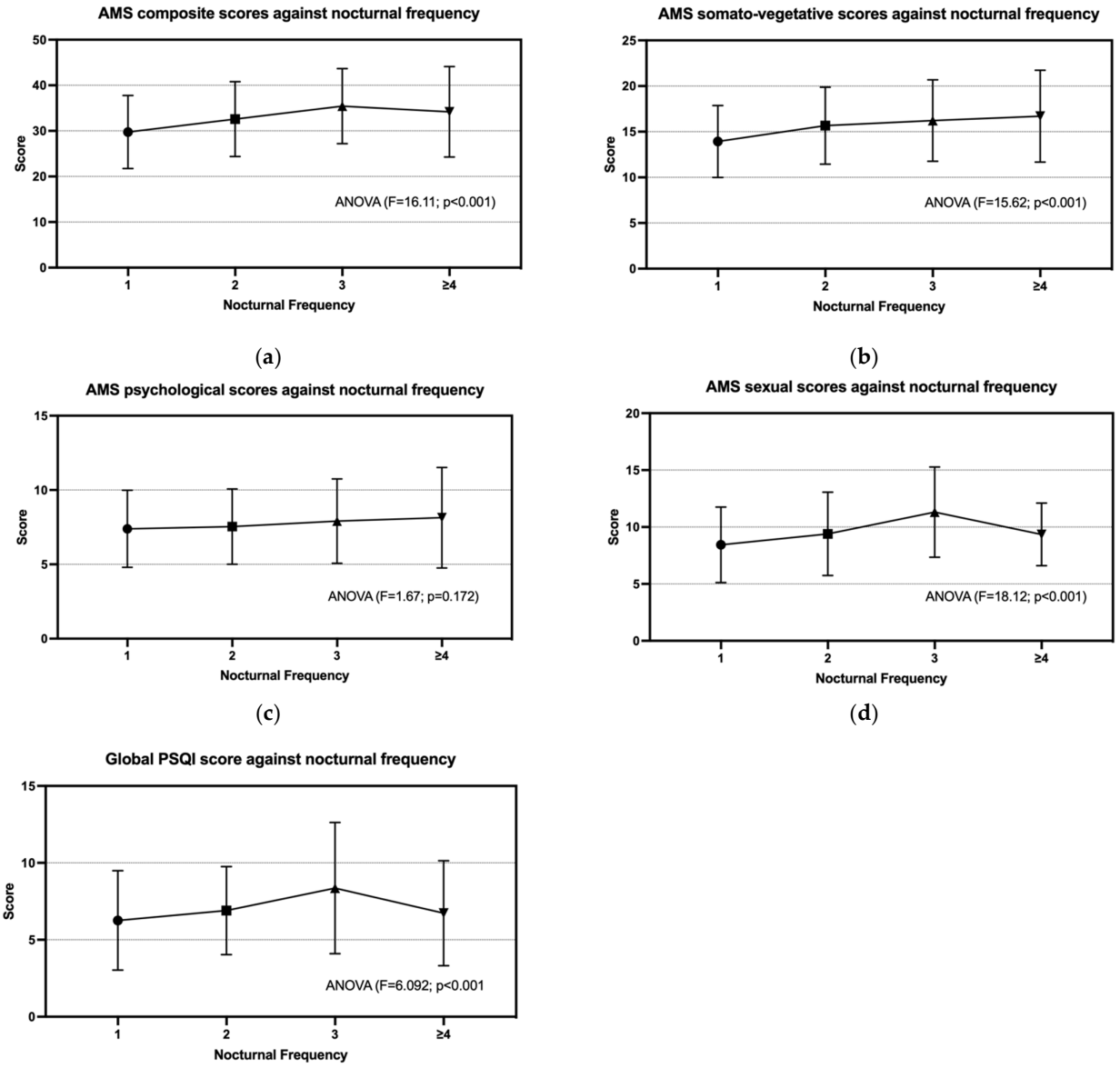

Figure 1. Severity of AMS and quality of sleep rated by the respondents with nocturia, are presented as the scores of: (a) composite AMS, (b) somato-vegetative AMS, (c) psychological AMS, (d) sexual AMS, and (e) global PSQI against the increasing nocturnal frequency.

In comparison, AMS was found to be more commonly *(p<0.001)* reported by the respondents with nocturia than those without, particularly with 25% at moderate level (versus 7% of non-nocturnal) and 3% at severe level (versus 0.4% of non-nocturnal) (Data not shown). The prevalence rates of moderate-to-severe levels of somato-vegetative, sexual, and psychological symptoms were measured as 68%, 61%, and 29%, respectively. As shown in Figure 1, the composite AMS, somato-vegetative, sexual and global PSQI scores shared similar significant upward trends (p<0.001) with increasing nocturnal frequency. , while all of them except the psychological domain were significantly (<0.001) varied among the nocturnal frequency levels. The linear increase of composite AMS scores was

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plateaued at 3 voiding episodes per night (Figure 1a). Over 80% of men having 3 voids per night were rated mild-to-moderate levels of AMS (about half and half in ratio) while the highest percentage of severe AMS was dominated among those of having ≥4 voids (Table 2). Although a clear increasing trend was observed with the advancing nocturnal frequency for the somato-vegetative symptom scores (Figure 1b), the percentage of clinically significant (i.e., moderate-to-severe) symptom level was increased from 60% to 76-80% discretely between those with 1 and ≥2 voiding frequency (Table 2). Psychological symptoms were the least affected by the nocturnal frequency, whereas a slight gradually increasing trend was observed for both the domain score (Figure 1c) and severity classification (Table 2). The prevalence of moderate-to-severe level of sexual AMS was peaked at 84.3% (51% were at severe level) among those with voiding frequency of 3 (Table 2). The sexual symptom score followed the trend observed in Global PSQI score that was linearly increased up to voiding frequency ≤3 and significantly dropped ($p<0.001$) at frequency ≥4 (Figure 1d & e). Interestingly, the percentage of poor sleeper was gradually decreased with the advancing nocturnal frequency (Table 2).

Table 2. Prevalence of different severity levels of composite AMS and its domains associated with nocturnal frequency.

AMS domains		Nocturnal frequency				χ^2
		1 time	2 times	3 times	≥4 times	p-value
		Number (Percentage)				
Composite	No/Little	170 (43.2)	71 (28.0)	12 (12.5)	8 (21.6)	<0.001
	Mild	151 (38.3)	102 (40.1)	37 (38.5)	18 (48.7)	
	Moderate	67 (17.0)	76 (29.9)	43 (44.8)	6 (16.2)	
	Severe	6 (1.5)	5 (2.0)	4 (4.2)	5 (13.5)	
Somato-vegetative	No/Little	20 (5.1)	11 (43.3)	5 (5.2)	3 (8.1)	<0.001
	Mild	143 (36.3)	51 (21.1)	14 (14.6)	5 (13.5)	
	Moderate	171 (43.4)	124 (48.8)	45 (46.9)	18 (48.7)	
	Severe	60 (15.2)	68 (26.8)	32 (33.3)	11 (29.7)	
Psychological	No/Little	116 (29.4)	47 (18.5)	20 (20.8)	10 (27.0)	0.002
	Mild	166 (42.1)	139 (54.7)	44 (45.8)	14 (37.9)	
	Moderate	94 (23.9)	58 (22.8)	23 (24.0)	7 (18.9)	
	Severe	18 (4.6)	10 (4.0)	9 (9.4)	6 (16.2)	
Sexual	No/Little	69 (17.5)	30 (11.8)	6 (6.3)	5 (13.5)	<0.001
	Mild	117 (29.7)	64 (25.2)	9 (9.4)	3 (8.1)	
	Moderate	130 (33.0)	76 (29.9)	32 (33.3)	18 (48.7)	
	Severe	78 (19.8)	84 (33.1)	49 (51.0)	11 (29.7)	

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Table 3. Correlation matrix for the nocturnal frequency, PSQI, ICIQ-Nqol and AMS variables amongst respondents with nocturia.

Variables	Nocturnal frequency	Global PSQI score	Nqol overall score	Nqol factor 1 score	Nqol factor 2 score	AMS composite score	AMS somato-vegetative score	AMS psychological score
AMS sexual subscale score	r=0.345; p=<0.001	r=0.248; p<0.001	r=0.228; p<0.001	r=0.190; p<0.001	r=0.212; p<0.001	r=0.775; p<0.001	r=0.476; p<0.001	r=0.417; p<0.001
AMS psychological score	r=0.168; p=<0.001	r=0.325; p<0.001	r=0.369; p<0.001	r=0.346; p<0.001	r=0.362; p<0.001	r=0.780; p<0.001	r=0.614; p<0.001	
AMS somato-vegetative score	r=0.391; p=<0.001	r=0.421; p<0.001	r=0.416; p<0.001	r=0.389; p<0.001	r=0.410; p<0.001	r=0.887; p<0.001		
AMS composite score	r=0.390; p=<0.001	r=0.408; p<0.001	r=0.424; p<0.001	r=0.386; p<0.001	r=0.411; p<0.001			
Nqol factor 2 score	r=0.253; p=<0.001	r=0.263; p<0.001	r=0.953; p<0.001	r=0.797; p<0.001				
Nqol factor 1 score	r=0.302; p<0.001	r=0.288; p<0.001	r=0.928; p<0.001					
Nqol overall score	r=0.295; p=<0.001	r=0.294; p<0.001						
Global PSQI score	R=0.320; P<0.001							

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3.2. NQoL score and voiding frequency are predictors for composite, somato-vegetative, and sexual AMS in. additon to age and PSQI score

Correlational analysis indicated that the composite AMS and domain scores were moderately inter-correlated with the nocturnal frequency (r=0.168-0.390; p<0.001), the Nqol overall score (r=0.228-0.424; p<0.001) as well as its factor scores (r=0.190-0.411; p<0.001), and the Global PSQI score (r=0.248-0.408; p<0.001) (Table 3). Stepwise multiple regression was performed separately with the composite AMS and three domains as dependent variables, whereas the independent variables were evaluated by the order of demographics and illnesses as 'block 1', nocturnal frequency and Nqol score as 'block 2', and Global PSQI score as 'block 3'. Multicollinearity was observed between the overall Nqol score and its two factor scores (with r=0.928-0.953; p<0.001), and therefore only Nqol score was evaluated by the stepwise multiple regression.

Table 4. Predictors of composite AMS and its domains identified by stepwise multiple regression.

AMS domains (Final model)	Predictors	b	SE	β	*p*-value	Adjusted R^2	Regression Significance
Composite	(Constant)	16.231	1.483		<0.001	0.335	<0.001
	NQoL score	0.252	0.036	0.273	<0.001		
	Global PSQI score	0.665	0.109	0.241	<0.001		
	Nocturnal frequency	1.267	0.338	0.161	<0.001		
	Hypertension (HTN)	1.427	0.757	0.081	0.060		
	Smoking habit	0.810	0.385	0.078	0.036		
	Diabetes mellitus (DM)	1.749	0.961	0.073	0.069		
	Age	0.036	0.023	0.065	0.120		
Somato-vegetative	(Constant)	7.354	0.758		<0.001	0.336	<0.001
	Global PSQI score	0.364	0.056	0.258	<0.001		
	Nqol score	0.120	0.019	0.253	<0.001		
	Nocturnal frequency	0.694	0.175	0.172	<0.001		
	Comorbidity (HTN+DM)	1.236	0.555	0.094	0.026		
	Smoking habit	0.488	0.197	0.092	0.014		
	Hypertension	0.478	0.405	0.053	0.238		
	Age	0.010	0.012	0.036	0.392		
	Benign prostatic hyperplasia	0.431	0.619	0.027	0.486		
Psychological	(Constant)	4.584	0.422		<0.001	0.188	<0.001
	NQoL score	0.080	0.012	0.291	<0.001		
	Global PSQI score	0.182	0.035	0.222	<0.001		
	Diabetes mellitus	0.459	0.295	0.065	0.121		
	Age	0.007	0.007	0.04`1	0.330		
Sexual	(Constant)	4.857	0.614		<0.001	0.166	<0.001
	Nocturnal frequency	0.655	0.154	0.204	<0.001		
	Gobal PSQI score	0.131	0.049	0.116	0.009		
	Hypertension	0.827	0.320	0.115	0.010		
	NQoL score	0.041	0.016	0.110	0.012		
	Age	0.020	0.011	0.089	0.058		

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As summarized in Table 4, based on the standardized coefficient (β) values, from strongest to weakness, the significant independent predictive factors identified for: 1) composite AMS were Nqol score, Global PSQI score, nocturnal frequency, HBP, smoking habit, DM and age; 2) somato-vegetative AMS were Global PSQI score, Nqol score, nocturnal frequency, comorbidity of DM and HBP, smoking habit, HBP, age and BPH; 3) psychological AMS were Nqol score, Global PSQI score, DM and age; and 4) sexual AMS were nocturnal frequency, Global PSQI score, HBP, Nqol score and age. Two demographic factors (age and smoking habits) and two metabolic illnesses (diabetes mellitus and high blood pressure) were identified as significant predictive factors for various AMS domains when examined in block 1. However, in the final regression models, independent variables entered in block 2 and block 3 were found to have stronger predictive values than those tested in block 1, whereas the predictive values of demographics and illnesses became weaker and less significant $p>0.05$ (Table 4). Whilst BPH was only predictive for the somato-vegetative and became the least significant predictor in the presence of nocturia and poor sleep quality (Table 4). The current models identified Nqol score and Global PSQI score as the two strongest predictors for the composite, somato-vegetative and psychological AMS (Table 6). In relation to the Nqol score, nocturnal frequency was also shown to be a significant predictor important for composite, somato-vegetative and sexual AMS (Table 4).

4. Discussion

This study found that many of the Hong Kong adult males living with nocturia were also comorbid with moderate-to-severe levels of somato-vegetative and sexual AMS, which impacted negatively on their HRQoL. Both NQoL and AMS questionnaires measure sleep quality that was believed to be interplayed between Nocturia and AMS among other factors such as age and certain age-related illnesses. NQoL factors, AMS severity and sleep quality were shown to be strongly intercorrelated with each other, whereas the current study has identified for the first-time that nocturnal factors including NQoL scores, voiding frequency, and sleep quality as strong predictors for the AMS. Whilst other well-known predictive risk factors for AMS were demonstrated to become weaker and less significant when those nocturnal factors were introduced into the regression models.

Clinically significant (Moderate-to-severe) levels of somato-vegetative (68%) and sexual (61%) AMS were more prevalent in the nocturnal population, as compared to more than 80% of general adult male population living in the city were having AMS at little-to-mild levels [11]. Nocturia commonly coexisted with age-related illnesses, in particular diabetes and hypertension were both characterized by increased urinary frequency and sleep fragmentation [25-26]. No doubt, aging and age-related illnesses have linked nocturia and AMS that are both were known to be associated with decline of androgen [12-14]. The consequences of testosterone deficiency in causing nocturia and sleep disturbance have been extensively reviewed by Shigehara et al. [27]. Nocturia was shown to be the only significant item of the International Prostate Symptom Score (IPSS) questionnaire that negatively correlated with the serum total testosterone in middle aged men [28]. Pathologically, the increase of night voiding frequency in aging men could also be due to the interference of diuresis and anatomical alteration of the lower urinary tract resulted from reducing androgen production, which in turn increased urine production during the night [29]. In this relation, the 'aging males' symptoms (AMS) scale was established to measure the symptoms of aging men and their impacts on health-related Quality of Life (HRQoL), based on the assumption that men would develop specific complaints during the aging process due to androgen deficiency [23]. The high prevalence of nocturia and its correlation with age [10] explained at least partly the high prevalence of AMS, whereas the strong inter-correlational relationships identified between the variables measured by the three questionnaires in this study further supported the cause-and-effect relationships that nocturia disturbs sleep to cause long-term consequence in harming physical and psychological health, hence affecting the overall HRQoL [30-32]. The strong correlations of PSQI with both ICIQ-NQoL and AMS scales as well as its independent predictive value

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on AMS suggested sleep quality was important for the HRQoL of men, whereas it also supported the assumption that the overall AMS-associated HRQoL could be modulated by sleep quality affected by nocturia. The ICIQ-NQoL alone measures the nocturia-specific QoL with the focus on two domains, namely bothersome and sleep disturbance [22]. However, the AMS assess further in general the somato-vegetative, psychological, and sexual well-beings of men [23]. The AMS scale consists of two items related to sleep disturbance, but none of the items asked about nocturia or related conditions. In the current study, the strong predictive values of Nqol, nocturnal frequency and sleep quality on AMS suggested the combination use of ICIQ-NQoL questionnaire and AMS scale for measuring the long-term impact on HRQoL of adult males. Otherwise, items could be added in the AMS scale to cover the nocturnal frequency and its bothersome level. The ICIQ-NoL has been proposed to be a useful tool for predicting the risk of fall [5], and therefore, the current findings support the same can be used for AMS.

The current study reports the first time the association between nocturia and AMS, which also identified nocturnal frequency as a significant predictor for AMS. However, biological markers should also be evaluated for establishing the interrelationship between nocturia and AMS. For instance, the nocturia should be precisely measured by using the frequencyvolume chart (FVC) over 2-3 days period [33]. Whereas serum testosterone [34] and melatonin [35] levels should also be included in the predictive model to represent the modulating effects of androgen deficiency and sleep disruption, respectively. More in-depth investigations using cohort study and interventional designs for further understanding the underlying pathology on how nocturia and AMS are related to aging are warranted.

5. Conclusions

Nocturia was demonstrated to be associated with clinically significant somato-vegetative and sexual AMS, which might be explained by the androgen deficiency that is implicated with aging and sleep quality. In particular, NQoL score and nighttime voiding frequency have impacted on the HRQoL of adult males, which were shown to be strong predictive factors for AMS. Current findings suggested the inclusion of nocturia when measuring the male-specific HRQoL related to aging.

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study. Written informed consent has been obtained from the patient(s) to publish this paper.

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