Analysis of changes in the pathophysiology of nocturia according to the number of nocturia episode, age, and gender using frequency volume charts
A retrospective observational study

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Abstract

Purpose: To evaluate the pathophysiology of nocturia based on the frequency volume chart, and determine the risk factors for nocturia occurring ≥2 times per night.

Materials and methods: In this retrospective study, we reviewed 311 patients with complaints of nocturia from January 2017 to February 2019 at our institution. Nocturnal polyuria (NP) and global polyuria (GP) were defined as NP index >0.35 regardless of age and 24 h urine volume >2.5 L/day, respectively. Decreased bladder capacity (dBC) was when the maximal voided volume was <325 mL. Decreased nocturnal bladder capacity (dNBC) was defined as nocturnal bladder capacity index >0.

Results: In total, 273 patients were included in the primary analyses. Of 802 days from 273 frequency volume charts, the median number of nocturia was 1 episode per day. Further, NP (odds ratios [OR] 7.01), GP (OR 4.25), dBC (OR 3.00), dNBC (OR 10.12), and age (OR 1.04) had the association with nocturia ≥2 times per night. There was a significant stepwise increase in NP, dNBC, dBC, and GP with the number of nocturia episodes. As patient age increased, the likelihood of NP ($P < 0.001$) and dBC ($P < 0.001$) being the cause for nocturia tended to increase, but that of dNBC ($P = 0.022$) and nocturia without cause ($P = 0.007$) tended to decrease. Moreover, dBC was more likely to cause nocturia in female patients than in male patients ($P < 0.001$).

Conclusion: NP, dBC, dNBC, and GP are important factors involved in the pathophysiology of nocturia occurring ≥2 times per night.

Abbreviations: 24hV = 24 hours voided volume, ANV = actual nocturnal voids, dBC = decreased bladder capacity, dNBC = decreased nocturnal bladder capacity, FVC = frequency volume chart, GP = global polyuria, IQR = interquartile range, MVV = maximal voided volume, NBCi = nocturnal bladder capacity index, Ni = nocturia index, NP = nocturnal polyuria, NPi = nocturnal polyuria index, NUV = nocturnal urine volume, PNV = predicted nocturnal void.

Keywords: frequency volume chart, nocturia, pathophysiology

1. Introduction

Nocturia, which means waking one or more times to void during sleeping, becomes especially bothersome for patients who have nocturia ≥ 2 times per night.[1] It is considered an important lower urinary tract symptom because of its increased prevalence with age.[2] A frequency volume chart (FVC), a noninvasive and objective tool, has been used for analyzing the pathophysiology of nocturia,[3,4] "Do the math" on several indices obtained from FVC can help differentiate between the different etiologies of nocturia.[5] Previous studies have explained the underlying pathophysiology using reduced bladder capacity (night and global), nocturnal polyuria (NP) and/or global polyuria (GP).[6–9] However, the pathophysiology of one-fourth of cases cannot

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be explained with these indices alone. Furthermore, there are no standard, pathophysiology-based diagnostic criteria to analyze the cause of nocturia, and there has been a lot of confusion in the analysis of nocturia using FVC, such as the consideration of NP and GP as the same etiology. Thus, another approach is needed to account for all pathophysiological processes underlying nocturia, and uniform definitions are required for each pathophysiological process included in its analysis.

In this study, we aimed to evaluate the pathophysiology of nocturia based on FVC, and determine risk factors for the occurrence of nocturia ≥ 2 times per night. Furthermore, we analyzed the change in these pathophysiological factors according to age, sex, and the number of nocturia episodes per night.

2. Materials and Methods

2.1. Study design

This was a retrospective observational study approved by our Institutional Review Board (IRB approval number: 2019-11-039). The requirement for informed consent was waived by the Institutional Review Board given the retrospective study design. We reviewed 311 patients who visited our hospital with complaints of nocturia and underwent FVC from January 2017 to February 2019. Inclusion criteria included completion of FVC for ≥ 24 h (the 24 hour-period beginning with the first morning void and ending with the first morning void the following day). Exclusion criteria included absence of nocturia on FVC and ≤ 24 h of FVC. We evaluated age, sex, FVC (sleep and waking time, voided volume, voided time, maximal voided volume [MVV], actual nocturnal voids [ANV], 24-hour voided volume [24hV], nocturnal urine volume [NUV]).

2.2. Study definitions

The 24hV and the NUV were defined according to International Continence Society terminology.[10] MVV was defined as the largest voided volume recorded in each FVC. From the FVC variables, we derived the nocturia index (Ni; NUV/MVV), NP index (NPi; NUV/24hV), predicted nocturnal void (PNV; Ni-1), and nocturnal bladder capacity index (NBCi; ANV-PNV). For this study, NP and GP were defined as NPi > 0.35 regardless of age and 24hV > 2.5 L/day, respectively. Decreased bladder capacity (dBC) was when the MVV was < 325 mL. Decreased nocturnal bladder capacity (dNBC) was defined as NBCi > 0.

2.3. Analyses

Patient characteristics are presented as frequencies and percentages for categorical variables or as median and interquartile range (IQR) for continuous variables. Multivariate binary logistic regression analysis was used to assess an association with ≥ 2 nocturia episodes per night. The etiology of nocturia was expressed using a Venn diagram of identified risk factors. In addition, serial changes in these risk factors were assessed according to the number of nocturia episodes, age, and sex. We used the linear-by-linear association test for the assessment of trends according to the number of nocturia episodes and age groups. The chi-square test was used to evaluate differences in the risk factors between sexes. Statistical significance was set at $P < .05$. SPSS version 25.0.0 (IBM Corp., Armonk, NY) was used for statistical analysis.

3. Results

3.1. Participants

A total of 311 patients were enrolled, of which 38 were excluded because 10 had no nocturia on FVC and 28 had incomplete or inaccurate FVC (Fig. 1). The remaining 273 patients were included in the primary analyses. Of these, 253 completed FVC for ≥ 3 days, 17 for 2 days and 3 for 1 day. The median age was 64 years (IQR 59–72) and 58.2% of the participants were male. Of the 802 days from 273 FVCs, the median number of nocturia episodes was 1 per day (IQR 1–2); 45.4% had 1, 27.8% had 2, 10.5% had 3, and 4.5% had 4 or more nocturia episodes per day (Appendix A, Supplemental Digital Content, http://links.lww.com/MD/H690). Table 1 shows details of the participants and their FVC characteristics. The median 24hV was 1800 mL (IQR 1360–2285) and median NUV was 600 mL (IQR 430–850).

3.2. Outcomes

NP (odds ratio [OR] 7.01, 95% confidence interval [CI] 4.69–10.47, $P < .001$), GP (OR 4.25, 95% CI 2.63–6.84, $P < .001$), dBC (OR 3.00, 95% CI 2.04–4.42, $P < .001$), dNBC (OR 10.12, 95% CI 6.77–15.12, $P < .001$), and age (OR 1.04, 95% CI 1.02–1.05, $P < .001$) had the association with nocturia occurring more than twice in one night (Table 2). Based on these factors, Figure 2 shows the etiology of nocturia [ANV ≥ 1 (a), ANV ≥ 2 (b)] from FVC.

There was a significant stepwise increase in NP, dNBC, dBC, and GP according to the number of nocturia episodes (NP $P < .001$; dNBC $P < .001$; dBC $P = .002$; GP $P < .001$, Fig. 3a). More frequent nocturia tended to have more contributory factors (≥2 contributed factors $P < .001$; ≥3 contributed factors $P < .001$, Fig. 3b). As the number of nocturia episodes increased, 23.6%, 62.6%, 83.5%, and 100% of patients with nocturia had ≥ 2 contributory factors, respectively, and 0.8%, 8.9%, 27.4%, and 72.9% had ≥ 3 factors, respectively.

As the patients' age increased, the likelihood of NP ($P < .001$) and dBC ($P < .001$) as a cause of nocturia tended to increase, but dNBC ($P = .022$) and nocturia without cause ($P = .007$) tended to decrease (Fig. 4a). In particular, dBC was the major cause in those aged ≤ 30 years. As age increased, the prevalence of nocturia with ≥ 2 causes ($P = .001$) and ≥ 3 causes ($P = .003$) tended to increase (Fig. 4b).

In female patients, dBC was more likely to cause nocturia than in male patients ($P < .001$). In the latter, the likelihood of GP increased with the number of nocturia episodes, unlike in female patients (male $P < .001$; female $P = 1.000$, Fig 5a). In those under 30 and over 80 years of age, the likelihood of NP increased among males, but that of dBC increased among females (Fig. 5b). In males, the likelihood of NP ($P = .002$) and dBC ($P < .001$) as the principal cause of nocturia tended to increase with age, but GP ($P < .001$) showed the opposite trend. Meanwhile, only NP ($P = .001$) and dBC ($P = .023$) showed a tendency to increase with age among females.

4. Discussion

Numerous reports have expounded on the etiology of nocturia by analyzing FVC findings. Varying results have been reported
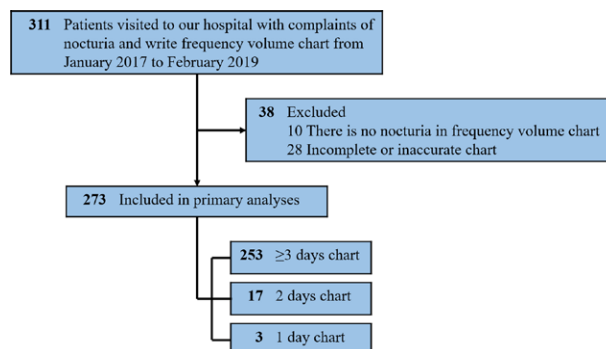

Figure 1. Overview of the study population.

Table 1

Participant characteristics.

Variables	
Age (years)	
Median	64
Range	23–85
IQR	59–72
Age group	
≤30s	11 (4.0%)
40s	19 (7.0%)
50s	56 (20.5%)
60s	106 (38.8%)
70s	62 (22.7%)
≥80s	19 (7.0%)
Sex (n, %)	
Male	159 (58.2%)
Female	114 (41.8%)
Number of nocturia episodes (per night)	1.5 ± 1.1
Median	1
Range	0–7
IQR	1–2
Sleep duration (min)	
Median	435
Range	130–745
IQR	385–490
24 h voided volume (mL)	
Median	1800
Range	135–5550
IQR	1360–2285
Nocturnal urine volume (mL)	
Median	600
Range	30–2400
IQR	430–850
Maximal voided volume during 1 day (mL)	
Median	330
Range	30–1600
IQR	300–450
Maximal voided volume during whole days (mL)	
Median	400
Range	40–1600
IQR	300–500

IQR = interquartile range.

Table 2

Multivariate binary logistic regression analysis of factors associated with 2 or more episodes of nocturia per night.

Variables	OR	95% CI	P-value
Age	1.04	1.02–1.05	<.001
Nocturnal polyuria	7.01	4.69–10.47	<.001
Decreased bladder capacity	3.00	2.04–4.42	<.001
Decreased nocturnal bladder capacity	10.12	6.77–15.12	<.001
Global polyuria	4.25	2.63–6.84	<.001
Sex (female vs male)	1.01	0.71–1.45	.939

CI = confidence interval, OR = odds ratio.

Figure 2. Venn diagram showing the etiology of nocturia [(a) actual nocturnal void ≥ 1, (b) actual nocturnal void ≥ 2]; NP = nocturnal polyuria, dBC = decreased bladder capacity, dNBC = decreased nocturnal bladder capacity, GP = global polyuria.

polyuria; both dBC and dNBC were considered as dBC). Based on our results, they should be considered as independent factors influencing the occurrence of nocturia, and should not be grouped together during analysis. A previous study explained that the etiology of nocturia was explained by its associated factors in only about 75% of cases,[11] but it is possible to explain the pathophysiology of nocturia occurring ≥ 2 times in around 99.7% of cases while using the four risk factors presented in this study. Therefore, it is very important to identify the above four factors in order to analyze nocturia using FVC.

As the number of nocturia episodes increases, so does the number of risk factors for nocturia. Two or more risk factors have an effect in > 60% of nocturia cases occurring ≥ 2 times, and 3 or more risk factors have an influence in > 70% of nocturia cases occurring ≥ 4 times. Previous studies have also shown that a combination of risk factors was involved as the number of nocturia episodes increased.[13,17,18] Therefore, a multi-pronged therapy is required to treat nocturia occurring ≥ 2 times per night. Notably, NP and dNBC play an important role in influencing the number of nocturia episodes. Therefore, physicians should be sufficiently prepared for NP and dNBC for the treatment of patients with severe nocturia.

due to population-based differences, but most have attributed nocturia to polyuria and decreased bladder capacity.[6,8,11–14] In this study, the factors associated with nocturia occurring ≥ 2 times per night were analyzed in particular, because patients with nocturia ≥ 2 times per night usually find their symptoms more bothersome.[1,15,16] This study showed that NP, dBC, dNBC, and GP had independent association with nocturia ≥ 2 times per night. Although these four have been discussed as risk factors for nocturia in previous studies, they have not been considered as independent factors in most cases, but grouped together and analyzed as one (for e.g., both GP and NP were considered as
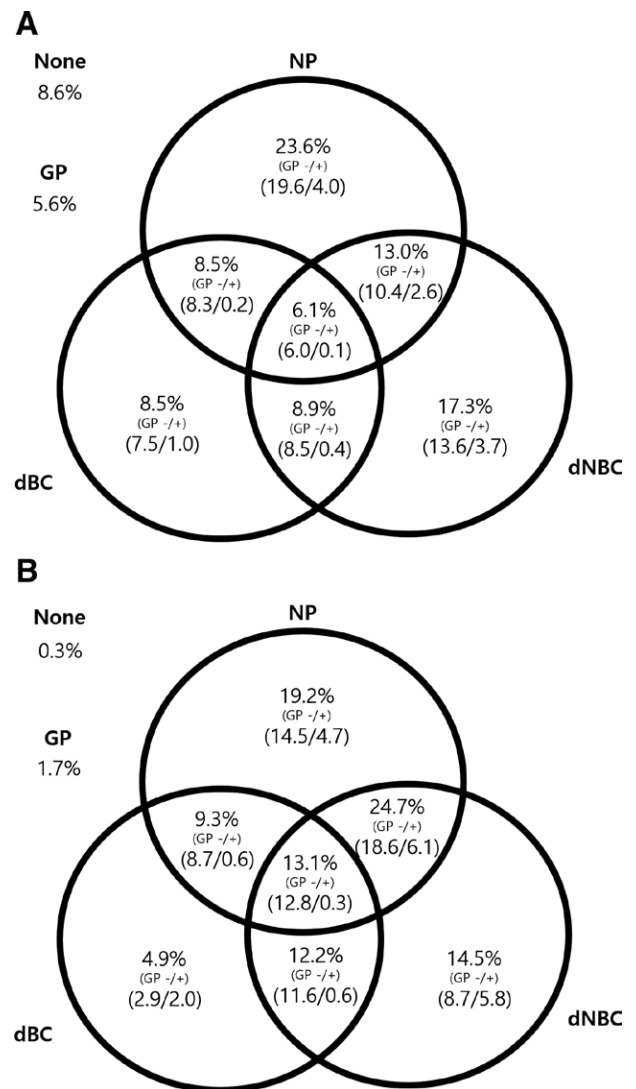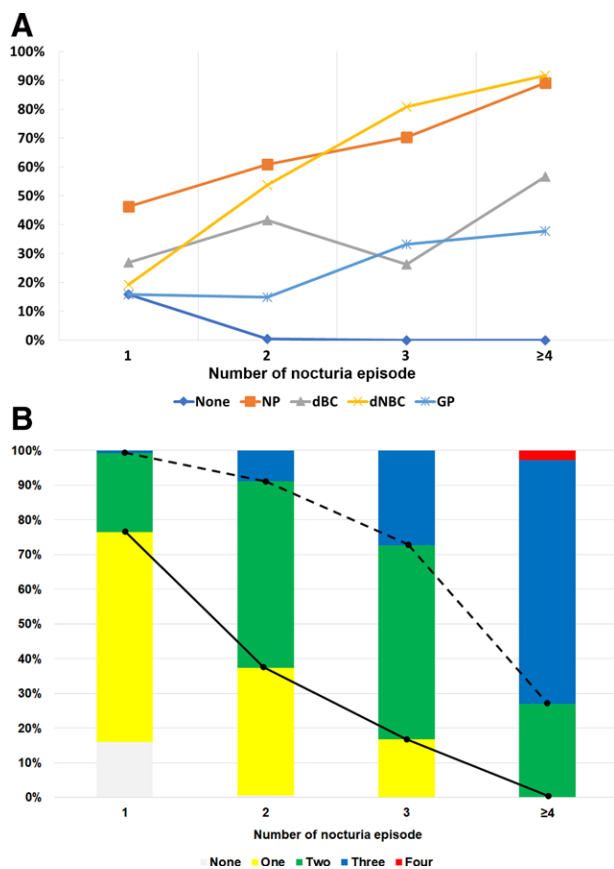
A

B

Figure 3. Changes in factors affecting nocturia according to the number of nocturia episodes. (a) Serial changes of each factor and (b) the number of factors according to nocturia episode (solid line: ≥2 factors; dotted line: ≥3 factors); NP = nocturnal polyuria, dBC = decreased bladder capacity, dNBC = decreased nocturnal bladder capacity, GP = global polyuria.

A

B

Figure 4. Changes in factors affecting nocturia according to age. (a) Serial changes of each factor and (b) the number of factors according to age (solid line: ≥2 factors; dotted line: ≥3 factors); NP = nocturnal polyuria, dBC = decreased bladder capacity, dNBC = decreased nocturnal bladder capacity, GP = global polyuria.

Numerous studies have shown that age is an important risk factor for nocturia.[2,4,19] The prevalence of nocturia reportedly increases with age in tandem with conditions such as cardiac disease and voiding problems.[13,14,20–22] Our study also showed that NP and dBC play an important role in the increased prevalence of nocturia with age. For this reason, the frequency of combined risk factors also increases with age, and NP and dBC play an important role in this increase. Interestingly, the frequency of dNBC as a risk factor for nocturia decreases with age, as reported in a previous study.[23] This is because NUV increases while MVV decreases with age, leading to an increase in PNV[NBCi = (ANV-PNV) = ANV-(Ni-1) = ANV-((NUV/MVV)-1], Appendix B, Supplemental Digital Content, http://links.lww.com/MD/H691). In this study, it was shown that age acts as an independent risk factor for nocturia in addition to the above four risk factors, indicating that there may be other factors that increase the prevalence of nocturia with age other than the above four risk factors. More research is needed to explore these factors.

Sex was not a risk factor for nocturia. However, the main etiology of nocturia differed according to sex. Similar to that shown in previous studies, polyuria, such as NP or GP, was a risk factor in males, while dBC was a risk factor among females.[13,24] For this reason, bias could occur due to gender differences, depending on the target group of the study. For example, the major risk factor of nocturia could be dBC when the target population is predominantly female.[8] In this study, the prevalence of nocturia due to NP or GP was high in males ≤ 30 years of age, which was possibly due to high water intake during the day and night, rather than any underlying disease.
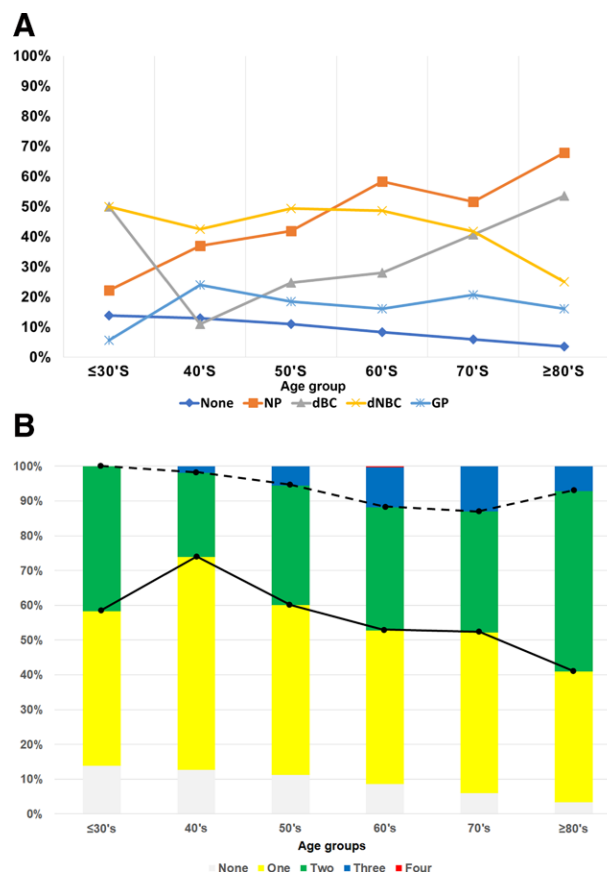
When analyzing nocturia using FVC, the classification criteria for each risk factor are important. However, studies on such classification criteria have not validated the choice of FVC variables or their diagnostic ranges. In this study, NP was classified as NPi > 0.35, dBC as MVV < 325 mL, dNBC as NBCi > 0, and GP as 24hV > 2.5 L/day. Notably, NP has been classified in various ways, which can be explained by its division into absolute criteria and age-adjusted criteria. The age-adjusted criteria, which has been widely used recently to analyze the etiology of nocturia using FVC, has two drawbacks. First, though the prevalence of NP according to age can be kept constant using these criteria, the increase in nocturnal urine volume according to age is not reflected. These criteria can be used for studies that analyze NP itself, but in studies analyzing the etiology of nocturia, it is necessary to reflect the increase in the nocturnal urine volume with age rather than diagnose NP. Second, since these criteria include age only up to 65 years, there is a possibility that the results could be disproportionately adjusted in studies that include many patients over 65 years of age. Therefore, it is more accurate to use absolute criteria for classification of NP when analyzing the etiology of nocturia, wherein more than half of the patients are ≥ 65 years of age, as in this study. There has not been yet a study that accurately describes the criteria for dBC. Previous studies using MVV < 200 mL, MVV < 250 mL, and MVV < 300 mL as the criteria for dBC have not explained the clear reason for this classification.[12,13,18] In this study, 325 mL, 65% of 500 mL, was set as the cutoff of dBC using the ICCS standard.[3] Further, previous studies describing the criteria for dNBC focused on determining the cutoff point reflecting the
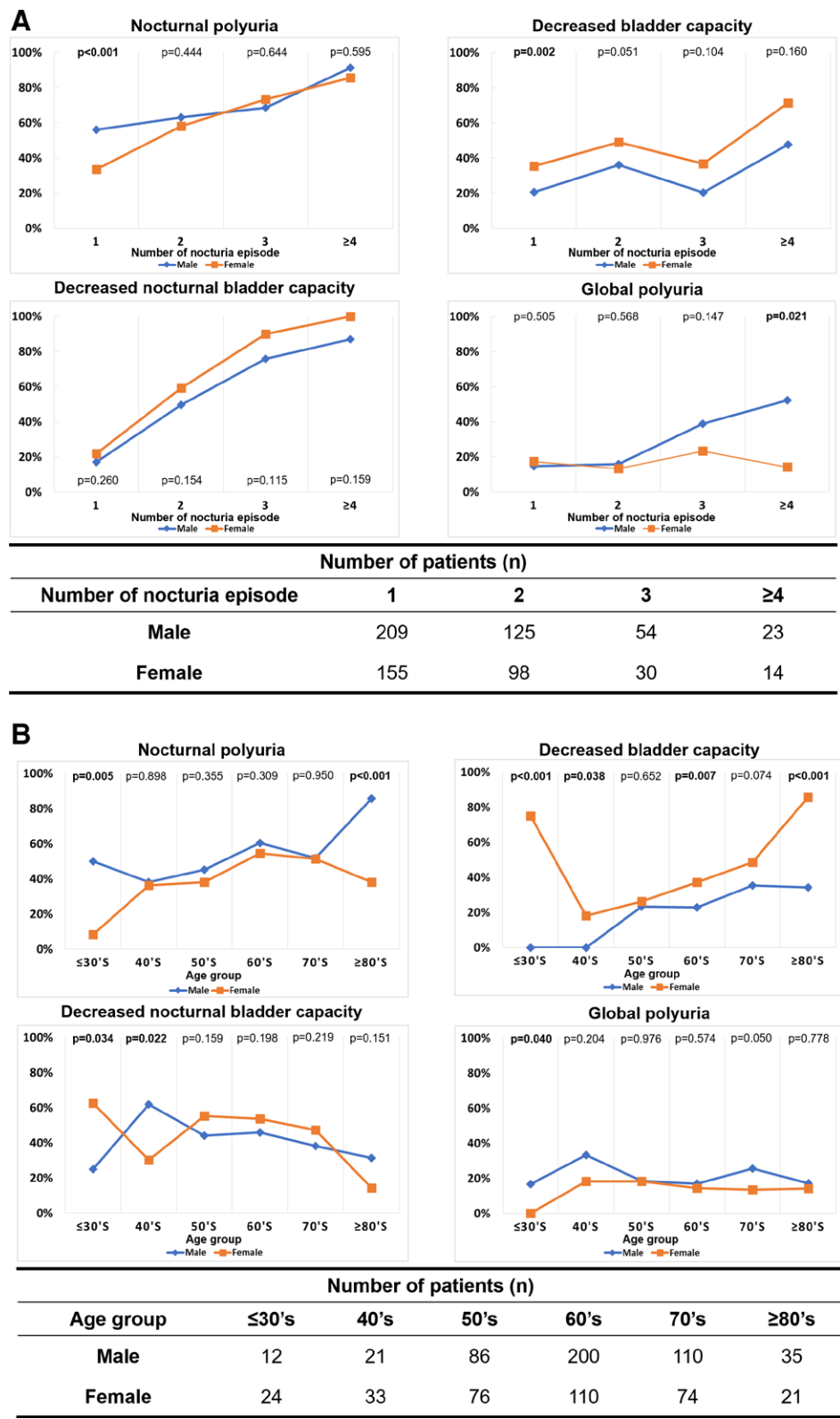
Figure 5. Sex-differences of serial changes of factors according to the number of nocturia episodes (a) and age (b). The statistical significance of the difference between sexes is expressed as the *P*-value.

severity of nocturia, rather than determining the classification criteria for dNBC. Since dNBC means that ANV is larger than PNV, NBCi > 0 was used as the criteria for dNBC. Absolute criteria were used to define GP rather than weight-adjusted criteria, because it is more effective in expressing large volumes of urine over 24 hour.

This study has several limitations. First, there is a possibility of selection bias because it is a retrospective study. In particular, the unusually high incidence of dBC in female patients ≤ 30 years of age is probably not a characteristic of this age group, but because most female patients who visited the department of urology with voiding problems had an overactive bladder.

Second, the severity of nocturia is low because the study participants were patients who visited the hospital with voiding problems as the chief complaint. Therefore, only about 43% experienced ≥ 2 nocturia episodes during FVC. However, this can also be considered a strength of the study, in that nocturia was analyzed without bias towards a specific disease such as overactive bladder or benign prostatic hypertrophy.

In conclusion, NP, dBC, dNBC, and GP are important pathophysiological processes involved in nocturia, and can be used to account for the etiology of most cases of nocturia occurring ≥ 2 times per night. As the number of nocturia episodes increase, NP and dNBC are the main causal factors, and the combination of these two is more likely to be involved in its pathophysiology. As age increases, NP in males and dBC in females are the major causes, while dNBC is the main cause in younger age groups.

Author contributions

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Visualization: Seong Cheol Kim, Kisoo Lee.
Writing-original draft: Seong Cheol Kim.
Writing-review & editing: Seong Cheol Kim, Ji Hyung Yoon.

References

[1] Coyne KS, Zhou Z, Bhattacharyya SK, et al.The prevalence of nocturia and its effect on health-related quality of life and sleep in a community sample in the USA. BJU Int. 2003;92:948–54.

[2] Chow PM, Liu SP, Chuang YC, et al. The prevalence and risk factors of nocturia in China, South Korea, and Taiwan: results from a cross-sectional, population-based study. World J Urol. 2018;36:1853–62.

[3] Austin PF, Bauer SB, Bower W, et al. The standardization of terminology of lower urinary tract function in children and adolescents: update report from the standardization committee of the international children's continence society. Neurourol Urodyn. 2016;35:471–81.

[4] Abrams P, Klevmark B. Frequency volume charts: an indispensable part of lower urinary tract assessment. Scand J Urol Nephrol Suppl. 1996;179:47–53.

[5] Weiss JP. Nocturia: "do the math". J Urol. 2006;175(3 Pt 2):S16–8.

[6] Epstein M, Blaivas J, Wein AJ, et al. Nocturia treatment outcomes: analysis of contributory frequency volume chart parameters. Neurourol Urodyn. 2018;37:186–91.

[7] Homma Y, Yamaguchi O, Kageyama S, et al. Nocturia in the adult: classification on the basis of largest voided volume and nocturnal urine production. J Urol. 2000;163:777–81.

[8] Presicce F, Puccini F, De Nunzio C, et al. Variations of nighttime and daytime bladder capacity in patients with nocturia: implication for diagnosis and treatment. J Urol. 2019;201:962–6.

[9] Weiss JP, Marshall SD. Nocturia. Campbell-Walsh Urology. 11th ed. 2016;1821–5:chap 78.

[10] Hashim H, Blanker MH, Drake MJ, et al. International continence society (ICS) report on the terminology for nocturia and nocturnal lower urinary tract function. Neurourol Urodyn. 2019;38:499–508.

[11] Kim ET. The etiology and classification of nocturia in adults. Korean J Urol. 2001;42:1075–9.

[12] Epstein MR, Monaghan T, Weiss JP. Etiology of nocturia response in men with diminished bladder capacity. Neurourol Urodyn. 2019;38:215–22.

[13] Goessaert AS, Krott L, Walle JV, Everaert K. Exploring nocturia: gender, age, and causes. Neurourol Urodyn. 2015;34:561–5.

[14] Klingler HC, Heidler H, Madersbacher H, Primus G. Nocturia: an Austrian study on the multifactorial etiology of this symptom. Neurourol Urodyn. 2009;28:427–31.

[15] van Dijk L, Kooij DG, Schellevis FG. Nocturia in the dutch adult population. BJU Int. 2002;90:644–8.

[16] Tikkinen KA, Johnson TM, 2nd, Tammela TL, et al. Nocturia frequency, bother, and quality of life: how often is too often? A population-based study in Finland. Eur Urol. 2010;57:488–96.

[17] Jeong JY, Kim SJ, Cho HJ, et al. Influence of type of nocturia and lower urinary tract symptoms on therapeutic outcome in women treated with desmopressin. Korean J Urol. 2013;54:95–9.

[18] Udo Y, Nakao M, Honjo H, et al. Analysis of nocturia with 24-h urine volume, nocturnal urine volume, nocturnal bladder capacity and length of sleep duration: concept for effective treatment modality. BJU Int. 2011;107:791–8.

[19] Tikkinen KA, Tammela TL, Huhtala H, Auvinen A. Is nocturia equally common among men and women? A population based study in Finland. J Urol. 2006;175:596–600.

[20] Bower WF, Whishaw DM, Khan F. Nocturia as a marker of poor health: causal associations to inform care. Neurourol Urodyn. 2017;36:697–705.

[21] Liu HY, Chung MS, Wang HJ, Liu RT, Chuang YC. Nocturia indicates a poor health status and increases mortality in male patients with type 2 diabetes mellitus. Int Urol Nephrol. 2016;48:1209–14.

[22] Madhu C, Coyne K, Hashim H, Chapple C, Milsom I, Kopp Z. Nocturia: risk factors and associated comorbidities; findings from the EpiLUTS study. Int J Clin Pract. 2015;69:1508–16.

[23] Weiss JP, Blaivas JG, Jones M, Wang JT, Guan Z, Study G. Age related pathogenesis of nocturia in patients with overactive bladder. J Urol. 2007;178:548–51.

[24] Rembratt A, Norgaard JP, Andersson KE. Differences between nocturics and non-nocturics in voiding patterns: an analysis of frequency-volume charts from community-dwelling elderly. BJU Int. 2003;91:45–50.