

## Circadian Rhythm of Voided Volume, Maximum Flow Rate, and Voiding Time Evaluated by Toilet Uroflowmetry in Hospitalized Women With Nocturia



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<b>OBJECTIVE</b>	To clarify the circadian rhythm of urination in hospitalized women with nocturia measured by toilet uroflowmetry and its age-related change.
<b>METHODS</b>	We evaluated 2602 urinations of 58 female patients (age, $68.4 \pm 15.2$ years) who were hospitalized in our institution for urological disease. We assessed voided volume (VV) as averages of every hour by generalized linear mixed models with an identity link function to adjust for personal bias and age. Maximum flow rate and voiding time were analyzed by the same method after adjustment for age, personal bias, and VV. We also compared these circadian rhythms between women $< 70$ and $\geq 70$ years.
<b>RESULTS</b>	VVs in the nighttime were significantly higher than that from 06:00-07:00 ( $205.6 \pm 11.7$ ml). Maximum flow rates in the afternoon were significantly higher than that from 06:00-07:00 ( $18.8 \pm 0.93$ ml/sec). Voiding time showed no statistically significant difference between the values at any time of day and that from 06:00-07:00. We also showed that the circadian rhythm of VV becomes less clear in the elderly women ( $P$ interaction = .0057). However, no significant difference was found in the maximum flow rate and voiding time regarding the pattern of the circadian rhythm between women $< 70$ and $\geq 70$ years old.
<b>CONCLUSION</b>	The present study clearly showed a circadian rhythm of VV and maximum flow rate in hospitalized women with nocturia. In addition, the pattern of the circadian rhythm of VV was attenuated in women $\geq 70$ years old. UROLOGY 179: 50–57, 2023. © 2023 Elsevier Inc. All rights reserved.

Nocturia was classically defined as “waking at night to void” by the International Continence Society in 2002.<sup>1</sup> A national survey in the United States with 5204 participants (mean age, 45.8 years) reported that at least 1 void occurred per night in 31%, and at least 2 voids occurred per night in 14.2%.<sup>2</sup> An epidemiological survey with 6517 Japanese participants (4568 men and 1949 women) showed that as many as 1856 individuals (28.5%) were diagnosed as having nocturia involving more than 2 voids per night.<sup>3</sup> This

survey also showed that cohorts of subjects aged 50-59, 60-69, and 70 years old or over had a prevalence of nocturia of, respectively, 1.75, 3.35, and 6.21 times that of the cohort aged 49 years or younger.<sup>3</sup> Thus, aging would appear to be 1 prominent risk factor for nocturia. Bladder outlet obstruction is another risk factor for nocturia, which has been noted in men with bladder outlet obstruction due to benign prostatic hyperplasia. However, bladder outlet obstruction is a condition observed even in women. Indeed, a retrospective review reported that 192 of 1014 women (19%) were diagnosed as having bladder outlet obstruction by urodynamic study, cystoscopy, and magnetic resonance imaging.<sup>4</sup> Furthermore, although stress urinary incontinence is considered the most bothersome of the lower urinary tract symptoms in women, nocturia is also known to be quite bothersome for them.<sup>5</sup> From the viewpoint of general health in women with nocturia, 1 report found that only 4.7% of women without nocturia reported poor

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health, whereas 11.2%, 20.1%, and 39.0% of women with 1, 2, and 3 or more voids per night, respectively, reported poor health.<sup>6</sup> Recently, it has become clear that nocturia is not merely related to health status and quality of life but also to life expectancy. Indeed, a population-based study of 784 Japanese subjects 70 years old or older reported that the mortality rate in subjects with nocturia was significantly higher than that in those without it.<sup>7</sup> A similar study with 9892 subjects (4758 men, 5134 women) showed a significant association between nocturia and all-cause mortality and mortality from cardiovascular disease.<sup>8</sup> When only women were analyzed in that study, moderate-to-severe nocturia was still significantly associated with mortality from all-causes and from cardiovascular disease.<sup>8</sup> Thus, there has been increased attention regarding the urinary status of women who complain of and are bothered by nocturia.

It is a well-known fact that circadian rhythm is involved in human physical activity, including various endocrinological secretions,<sup>9</sup> renal function,<sup>10</sup> blood pressure,<sup>11</sup> heart function,<sup>12</sup> and cancer occurrence and progression.<sup>13</sup> As bladder function also naturally fluctuates during the day, the state of urination also differs depending on the time of day. We previously evaluated the circadian rhythm of urination in a group of hospitalized male patients with nocturia evaluated by toilet uroflowmetry (UFM) over a 24-hour period and reported that voided volume (VV) was significantly higher in the nighttime than that in the daytime after adjustment for age.<sup>14</sup> We also reported that the maximal flow rate (MFR) from 06:00-09:00, especially just after waking up, was lowest, and voiding time at nighttime was significantly longer than that in the morning even after adjustment for age and VV. According to these results, we speculated that urine disruption and terminal dribbling are likely to occur during the nighttime in men with nocturia. However, no studies of the circadian rhythm of urination in women with nocturia have been reported, to our knowledge. Because the lower urinary tract of women is anatomically different from that of men, we hypothesized that the circadian rhythm of urination in women with nocturia would differ from that of the men shown in our previous study.<sup>14</sup>

In the present study, the urination parameters of MFR, VV, and voiding time were analyzed by toilet UFM, which is more representative of the patients' ordinary urination, in hospitalized women with nocturia over a full 24-hour period to clarify the circadian rhythm of urination.

## MATERIALS AND METHODS

In this retrospective study, we included 58 female patients who were hospitalized in our institution for urological disease from December 2018 to January 2020. Patients with neurogenic bladder, renal failure, urinary tract infection, and absence of nocturnal voiding were excluded from this study. Patients taking diuretics on a regular basis were also excluded. Our

subjects were hospitalized for the careful examination of hematuria in 33 women (12 with bladder tumor, 9 with renal tumor and 12 with renal pelvic/ureteral tumor, according to the final diagnosis determined later), for examination of hydronephrosis in 13 women, for conservative treatment for urolithiasis in 8 women and for other reasons in 4 women. Comorbidities were found for hypertension in 20 women, hyperlipidemia in 16 women and diabetes in 4 women (there was patient overlap). Only 1 patient had taken medication of mirabegron and/or imidafenacin for lower urinary tract symptoms. Finally, from the database of our UFM records, the data of 2602 urinations evaluated by toilet UFM (UM-100, TOTO Ltd., Tokyo, Japan) were included in this study. Among these 58 patients, 25 patients (43.1%) were diagnosed as having nocturnal polyuria.

First, we performed the same method of analysis as done in our previous study with men.<sup>14</sup> In brief, records including VV, MFR, and voiding time were evaluated as averages over every hour. We statistically evaluated the mean values at each time of the day after adjusting for age and personal bias by statistical ingenuity as in our previous study because the recorded number of urinations varied widely depending on the person ( $44.9 \pm 84.9$  times per person). After adjustment for these factors, VV of each time period was analyzed to compare it with the value from 06:00-07:00. The same comparisons were also performed for MFR after adjustment for age, personal bias, and VV because MFR usually varies with the value of VV. Voiding time was also evaluated by the same method as for MFR. Thereafter, to clarify the effect of aging, we compared the circadian rhythm between 1190 urinations of 26 women < 70 years old and 1412 urinations of 32 women  $\geq 70$  years old.

This study was carried out in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. Informed consent was obtained in the form of opt-out on the hospital's website. The procedures were approved by the Regional Ethics Committee of Juntendo Urayasu Hospital, Urayasu, Japan (approval number: 2019-022).

## Statistical Analysis

We used generalized linear mixed models with an identity link function to evaluate the association between VV, MFR, and voiding time accounting for multiple UFM examinations, by which we could ignore individual deviations in the number of urinations and other covariates. To compare the circadian rhythm between women < 70 years and  $\geq 70$  years old, the interaction between age and time was analyzed by generalized linear mixed models. Patient background data are presented as the mean  $\pm$  standard deviation, and data on urination are presented as the mean  $\pm$  standard error. A *P* value < .05 was considered statistically significant. Statistical analyses were performed with SPSS version 24.0 (SPSS Inc., Chicago, IL).

## RESULTS

Patients' characteristics and VV, MFR, and voiding time are summarized in Table 1. The mean age of our 58 patients was  $68.4 \pm 15.2$  years, and the number of incidents of nocturia was  $2.5 \pm 1.1$ . VV, MFR, and voiding time obtained by UFM were calculated as the mean of each of the 24 1-hour time periods of the day. The number of urinations of each period varied from 64 (2.5%) during 22:00-23:00 to 173 (6.6%) during 17:00-18:00. The records of VV after adjustment for age are summarized in Table 2 and Figure 1A. VVs from 00:00-01:00

**Table 1.** Patient background data.

Patients, n	58	
Age (y), mean $\pm$ SD	68.4 $\pm$ 15.2	(18-92)
Total no. of urinations	2602 (100.0%)	
06:00-07:00	147 (5.6%)	
07:00-08:00	105 (4.0%)	
08:00-09:00	101 (3.9%)	
09:00-10:00	78 (3.0%)	
10:00-11:00	84 (3.2%)	
11:00-12:00	96 (3.7%)	
12:00-13:00	99 (3.8%)	
13:00-14:00	79 (3.0%)	
14:00-15:00	130 (5.0%)	
15:00-16:00	114 (4.4%)	
16:00-17:00	134 (5.0%)	
17:00-18:00	173 (6.6%)	
18:00-19:00	129 (5.0%)	
19:00-20:00	115 (4.5%)	
20:00-21:00	169 (6.5%)	
21:00-22:00	97 (3.7%)	
22:00-23:00	64 (2.5%)	
23:00-24:00	101 (3.9%)	
00:00-01:00	99 (3.8%)	
01:00-02:00	94 (3.6%)	
02:00-03:00	73 (2.8%)	
03:00-04:00	89 (3.4%)	
04:00-05:00	109 (4.2%)	
05:00-06:00	124 (4.8%)	
Voided volume (ml)	182.4 $\pm$ 104.3	(50.1-850.9)
Maximum urinary flow (ml/s)	18.6 $\pm$ 9.3	(3.9-65.2)
Voiding time (s)	33.9 $\pm$ 53.0	(3.6-593.6)
Nocturia, n	2.5 $\pm$ 1.1	(1-5)

Values are expressed as n (percent) or mean  $\pm$  SD (range), unless otherwise noted.

(253.8  $\pm$  12.6 ml,  $P < .01$ ), 02:00-3:00 (265.3  $\pm$  13.5 ml,  $P < .01$ ), 03:00-4:00 (250.2  $\pm$  12.9 ml,  $P < .05$ ) to 04:00-05:00 (256.9  $\pm$  12.3 ml,  $P < .01$ ) were significantly higher

**Table 2.** Uroflowmetry parameters for each 1-h time period.

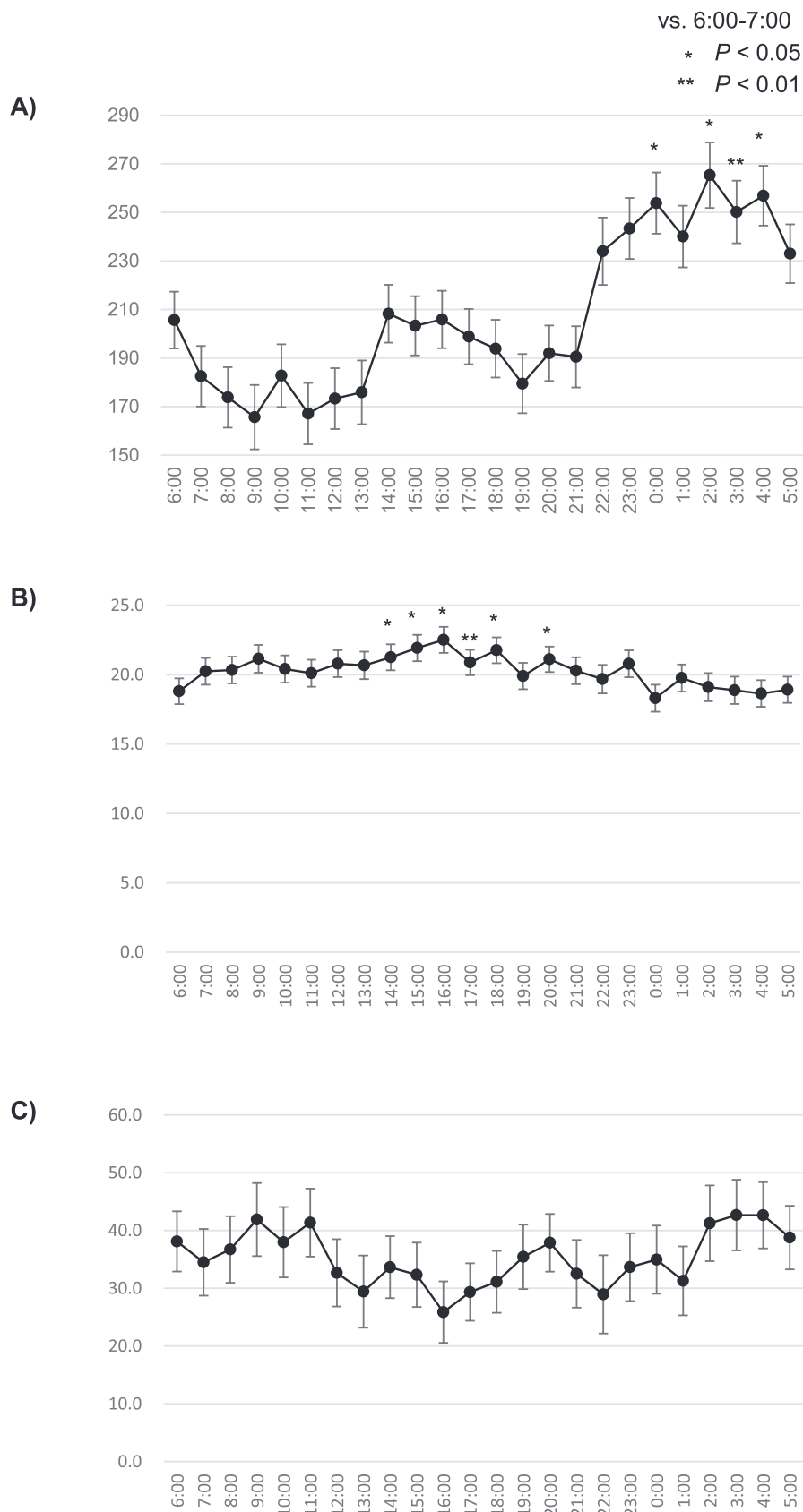
Time Period	Voided Volume (ml)	Maximal Flow Rate (ml/s)	Voiding Time (s)
06:00-07:00	205.6 $\pm$ 11.7	18.8 $\pm$ 0.93	38.1 $\pm$ 5.2
07:00-08:00	182.5 $\pm$ 12.5	20.2 $\pm$ 0.96	34.5 $\pm$ 5.8
08:00-09:00	173.8 $\pm$ 12.5	20.3 $\pm$ 0.96	36.7 $\pm$ 5.8
09:00-10:00	165.7 $\pm$ 13.3	21.1 $\pm$ 1.00	41.9 $\pm$ 6.3
10:00-11:00	182.8 $\pm$ 12.9	20.4 $\pm$ 0.98	38.0 $\pm$ 6.1
11:00-12:00	167.1 $\pm$ 12.6	20.1 $\pm$ 0.97	41.4 $\pm$ 5.9
12:00-13:00	173.3 $\pm$ 12.5	20.8 $\pm$ 0.97	32.7 $\pm$ 5.8
13:00-14:00	175.9 $\pm$ 13.1	20.7 $\pm$ 0.99	29.4 $\pm$ 6.3
14:00-15:00	208.2 $\pm$ 11.9	21.3 $\pm$ 0.94	33.6 $\pm$ 5.4
15:00-16:00	203.3 $\pm$ 12.2	21.9 $\pm$ 0.95	32.3 $\pm$ 5.6
16:00-17:00	205.9 $\pm$ 11.8	22.5 $\pm$ 0.94	25.9 $\pm$ 5.3
17:00-18:00	198.9 $\pm$ 11.4	20.9 $\pm$ 0.92	29.3 $\pm$ 5.0
18:00-19:00	193.9 $\pm$ 11.9	21.8 $\pm$ 0.94	31.1 $\pm$ 5.3
19:00-20:00	179.5 $\pm$ 12.2	19.9 $\pm$ 0.95	35.4 $\pm$ 5.6
20:00-21:00	192.0 $\pm$ 11.4	21.1 $\pm$ 0.92	37.9 $\pm$ 5.0
21:00-22:00	190.5 $\pm$ 12.6	20.3 $\pm$ 0.97	32.5 $\pm$ 5.9
22:00-23:00	234.0 $\pm$ 13.9	19.7 $\pm$ 1.03	28.9 $\pm$ 6.8
23:00-24:00	243.4 $\pm$ 12.6	20.8 $\pm$ 0.97	33.7 $\pm$ 5.9
00:00-01:00	253.8 $\pm$ 12.6	18.3 $\pm$ 0.97	34.9 $\pm$ 5.9
01:00-02:00	240.1 $\pm$ 12.7	19.8 $\pm$ 0.98	31.3 $\pm$ 6.0
02:00-03:00	265.3 $\pm$ 13.5	19.1 $\pm$ 1.01	41.2 $\pm$ 6.5
03:00-04:00	250.2 $\pm$ 12.9	18.9 $\pm$ 0.99	42.7 $\pm$ 6.1
04:00-05:00	256.9 $\pm$ 12.3	18.6 $\pm$ 0.96	42.6 $\pm$ 5.7
05:00-06:00	233.0 $\pm$ 12.1	18.9 $\pm$ 0.95	38.8 $\pm$ 5.5

than that from 06:00-07:00 (205.6  $\pm$  11.7 ml). The lowest VV was observed during 09:00-10:00 (165.7  $\pm$  13.3 ml), but even so, there was no statistically significant difference from the value for 06:00-07:00. The highest VV was observed during 02:00-03:00 (265.3  $\pm$  13.5 ml). Regarding the circadian rhythm, VV showed a gradual decrease after waking, an increase in the afternoon, and the greatest increase during the nighttime hours. The MFRs from 14:00-15:00 (21.3  $\pm$  0.94 ml/sec,  $P < .01$ ), 15:00-16:00 (21.9  $\pm$  0.95 ml/sec,  $P < .01$ ), 16:00-17:00 (22.5  $\pm$  0.94 ml/sec,  $P < .01$ ), 17:00-18:00 (20.9  $\pm$  0.92 ml/sec,  $P < .05$ ), 18:00-19:00 (21.8  $\pm$  0.94 ml/sec,  $P < .01$ ) to 20:00-21:00 (21.1  $\pm$  0.92 ml/sec,  $P < .01$ ) were significantly higher than that from 06:00-07:00 (18.8  $\pm$  0.93 ml/sec; [Table 2](#), [Fig. 1B](#)). The lowest MFR was observed during 00:00-01:00 (18.3  $\pm$  0.97 ml/sec), but there was no statistically significant difference from the value for 06:00-07:00. The highest MFR was observed during 16:00-17:00 (22.5  $\pm$  0.94 ml/sec), which indicates that MFR showed circadian rhythm, being higher in the afternoon until bedtime. For voiding time, there was no statistically significant difference between the values at any time of day and that at 06:00-07:00 ([Table 2](#), [Fig. 1C](#)).

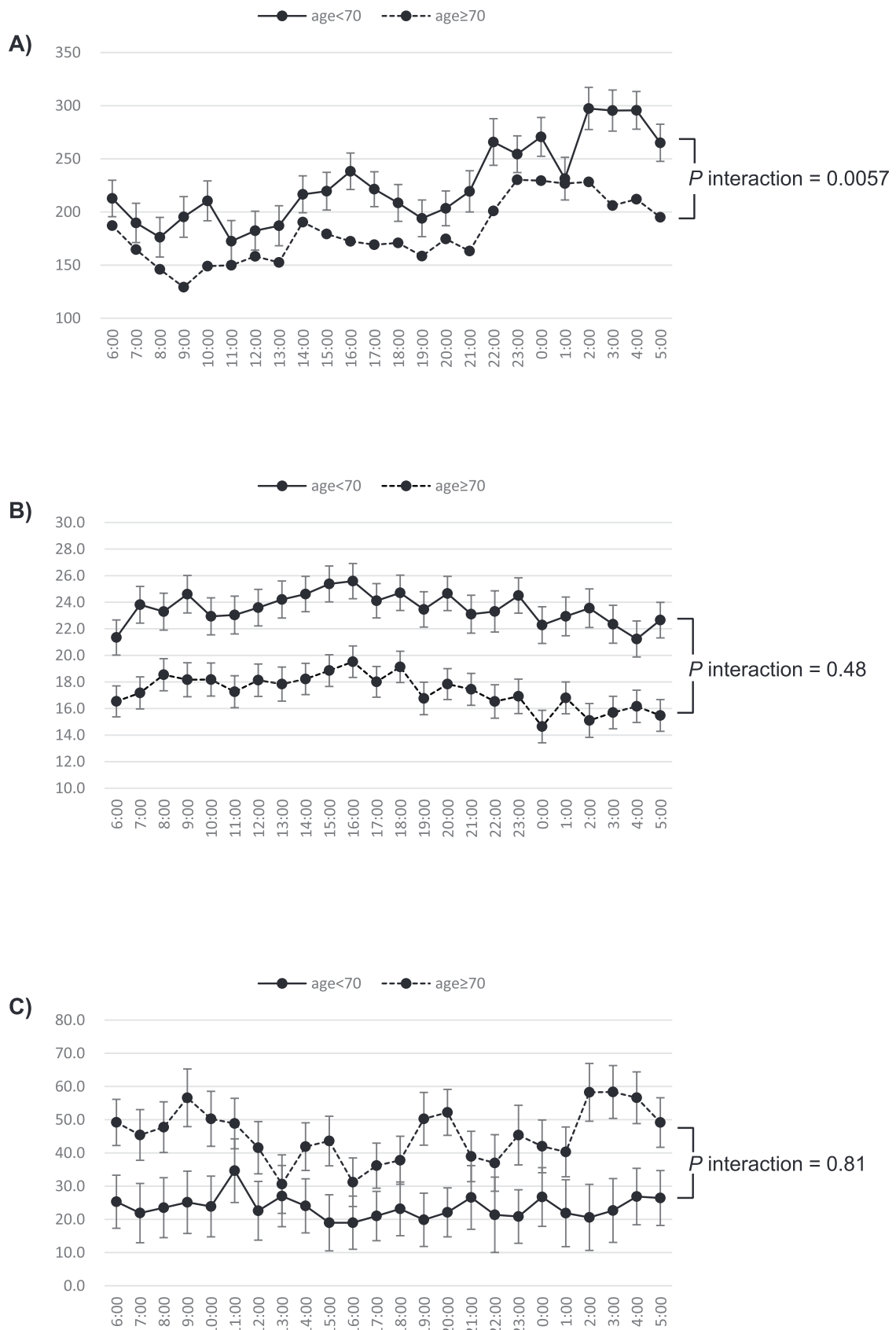
To examine the effect of aging, we compared the circadian rhythm of VV, MFR, and voiding time between women  $< 70$  and  $\geq 70$  years old and found only VV to be affected by aging. In other words, the circadian rhythm of VV, which increases at night, was found to slow down in those  $\geq 70$  years old ([Fig. 2](#)).

## COMMENT

In general, there are sex differences in the effect of aging on urinary function. In aging men, symptoms are primarily due to an enlarged prostate, whereas urinary incontinence, especially urgency, is often bothersome in aging women. Nocturia is a common symptom of



**Figure 1.** The circadian rhythm of voided volume after adjustment for age **(A)**. The circadian rhythm of maximum flow rate **(B)** and voided volume **(C)** after adjustment for age and voided volume.



**Figure 2.** Comparison of the circadian rhythm of voided volume (VV) after adjustment for age (**A**), maximum flow rate after adjustment for age and VV (**B**) and voiding time after adjustment for age, and VV (**C**) between the women <70 and ≥70 years old. Only the circadian rhythm of VV was found to slow down in the women ≥70 years old (*P* interaction = .0057).

bothersome lower urinary tract symptoms seen in both men and women, but there have been no reports on the circadian rhythm of urination in women with nocturia. In the present study, we showed that the mean values of VV, MFR, and voiding time were 182.4 ml, 18.6 ml/sec, and 33.9 sec, respectively, from the evaluation of 2602 urinations in the database of our UFM records. Regarding UFM in women, there have been several reports for VV, MFR, and voiding time. A meta-analysis with 11 studies regarding VV and MFR and 7 studies regarding voiding time showed that VV, MFR, and voiding time in healthy women were 324 ml, 29 ml/sec, and 28 sec, respectively.<sup>15</sup> Another previous review reported that VV and MFR were  $338 \pm 161$  ml and  $23.5 \pm 10$  ml/sec, respectively.<sup>16</sup> Compared with those data, the mean values of VV (182.4 ml) and MFR (18.6 ml/sec) in the present study were relatively low. These discrepancies were mainly caused by the difference in subject background. Indeed, the previous studies focused on healthy women, whereas ours addressed women with several urological problems and nocturia. Furthermore, our subjects had several co-morbidities, such as hypertension and diabetes, which were already reported to be associated factors for more than 2 voids per night in women by a cross-sectional and population-based study.<sup>17</sup> In addition, our subjects were relatively old ( $68.4 \pm 15.2$  years) as an age of 60 years or over was also associated with more than 2 voids per night in women in the previous study.<sup>17</sup> Therefore, unlike previous studies of relatively young healthy women, the present study is, to our knowledge, the first analysis of circadian rhythm of urination in women, albeit in a limited population of relatively elderly hospitalized women with some urologic problems or co-morbidities.

In the present study, VV showed a gradual decrease after waking, an increase in the afternoon, and the greatest increase during the nighttime hours. The finding that VV was significantly higher in the nighttime than daytime was basically consistent with previous studies based on a 3-day frequency volume chart in both men and women,<sup>18</sup> a 24-hour self-made UFM system in men,<sup>19</sup> home UFM in men,<sup>20</sup> and toilet UFM in the men in our previous study.<sup>14</sup> As people generally feel less need to urinate when they sleep soundly, it is assumed that VV trends to be greater during sleep. Thus, our results regarding the circadian rhythm of VV seem reasonable. However, patients with nocturia are also known to feel the usual urge to urinate due to shallow sleep, and VV could be smaller as a result of their frequent urinations.<sup>21</sup> Furthermore, it has been reported that with advancing age, both a decrease in bladder capacity and an increase in nocturnal urine volume become more pronounced, and nocturia caused by this decrease in bladder capacity is more pronounced in women than in men.<sup>22</sup> Indeed, women  $\geq 70$  years old had smaller VV than women  $< 70$  years at all-time points in the present study. Furthermore, we clearly showed that the circadian rhythm of VV becomes less clear in the elderly women (Fig. 2A). We

assume that the reason for this finding relates to the characteristic of decreased distensibility with age,<sup>23</sup> which is more pronounced during nighttime. In fact, in the present study, VV tended to decrease with age (data not shown), as in the previous reports.<sup>24,25</sup>

In our previous study of men, MFR was most depressed during the morning waking hours, that is, 06:00-09:00,<sup>14</sup> but the present study of women showed a distinctly different circadian rhythm in which the lowest MFR was found at midnight, that is, 00:00-01:00. Furthermore, MFR was generally higher in the afternoon until bedtime than in the daytime. This phenomenon of MFR elevation in the afternoon was also observed in our previous study of circadian rhythms of MFR in men. It is speculated that the switch from parasympathetic to sympathetic nervous system is insufficient at the time of waking, and that the gradual improvement of this switch leads to an increase in MFR during the afternoon. Another factor that may have a significant influence on MFR is that abdominal pressure may become easier to apply in the afternoon. When humans sleep, they are relaxed with the parasympathetic nervous system being dominant, and after waking up, dominance immediately switches to the sympathetic nervous system and they become more active.<sup>26</sup> It is speculated that this sympathetic nervous system-dominant state is naturally more prone to causing abdominal pressure than the parasympathetic nervous system-dominant state. When the effect of age was evaluated, the women  $\geq 70$  years old had a lower MFR than those  $< 70$  years old at all-time points, but there was no difference between them in their pattern of circadian rhythm. This means that the MFR of elderly women is similarly declining regardless of the time of day. Finally, we found no evidence of circadian rhythm in voiding time. We speculated in our previous study that men tend to urinate longer due to nocturnal urinary disruption and terminal dribbling, but we did not observe this symptom in women. In fact, this may be the reason why we did not find circadian rhythm to be significant. Furthermore, although voiding time was longer in the women  $\geq 70$  years old vs those  $< 70$  years old at all-time points, there was no difference in the pattern of circadian rhythm between the two groups. In other words, voiding time in elderly women is expected to be similarly long at all-times of the day.

The present study has some limitations. First, our study included patients who were admitted to hospital before a definite diagnosis was made but who were ultimately treated at a later date for malignant disease. Thus, we cannot rule out that the urinary pattern of these patients might be slightly different than that of the general female population. Second, comorbidities such as hypertension, diabetes, and hyperlipidemia might be related to urinary function because this study was conducted retrospectively. Third, hospitalized patients may sleep differently than they do at home, as we pointed out in our previous study with hospitalized men<sup>14</sup>. Patients may wake up more during the night due to environmental



changes, such as the breathing, talking, or snoring of other patients in the same room, noise from medical equipment, or their own symptoms, such as pain or discomfort.<sup>27</sup> This increased mid-onset arousal may have increased the frequency of nocturnal voiding, which may have differed from the normal pattern of urination.<sup>28</sup>

## CONCLUSION

The present study of the urination parameters of hospitalized women with nocturia by toilet UFM over a 24-hour period showed the circadian rhythm of VV and MFR. The VV decreased after waking and increased from the afternoon, with the greatest increase occurring during the nighttime hours. This study also showed that the circadian rhythm of VV became less clear in the elderly women. Further, the circadian rhythm of MFR was higher in the afternoon until bedtime. The lowest MFR was found during 00:00–01:00, in sharp contrast to the previous result in men. However, the patterns of circadian rhythm in MFR did not change much, even in the elderly women. Due to several limitations, we cannot rule out the possibility that this study does not represent the circadian rhythm of urination in the general female population. Nevertheless, the present data are the first to show circadian rhythm in urination of women with nocturia and are highly valuable as real-world data.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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